The explanation of apoplexy (1550-1700)

master's thesis in the History and Philosophy of Science

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Es ist sehr schwer, wenn überhaupt möglich, die Geschichte eines Wissensgebietes richtig zu beschreiben. Sie besteht aus vielen sich überkreuzenden und wechselseitig sich beeinflussenden Entwicklungslinien der Gedanken, die alle erstens als stetige Linien und zweitens in ihren jedesmaligen Zusammenhange mit einander darzustellen wären. ... Wir müssen die zeitliche Stetigkeit der beschriebenen Gedankenlinie immer wieder unterbrechen, um andere Linien einzuführen; die Entwicklung aufhalten, um Zusammenhänge besonders darzustellen; vieles weglassen, um die idealisierte Hauptlinie zu erhalten.[1]

The illustration on the title page of this thesis is the frontispiece of Domenico Mistichelli's 'Trattato dell' Apoplessia'*, published in 1709 in Rome. The central object of the engraving is the corpse of a patient, who has supposedly died from apoplexy. The top part of his skull has been removed; part of his face, right shoulder and trunk are visible. Three persons surround his body: two women, one of whom is applying what looks like a magnifying glass, and a man in Greek garments, perhaps Hippocrates. The woman to the right of this scene, holding a candle, probably represents wisdom; the soldier to the left may signify courage. The three running figures in the background are probably trying to escape the disease. Above, two deities reside on a cloud. The left person, wearing a laurel crown, is presumably Apollo. The right celestial being, with a forge depicted behind him, must be Vulcan; the branding iron he is holding has a role in a mode of treatment the author of the book proposes. Putti surround the scenes.*

word count (without footnotes, appendix & references)

- original text	34.382
- citations (translated)	11.525
- figure legends	2.328
- boxes (biographies)	2.955
total	51.190

[1] Fleck (1980 [1935]), *Entstehung einer Tatsache*, 23.

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PREFACE

The subject of this thesis is the early history of apoplexy, a category of disease recognised in antiquity on the basis of its manifest symptoms. It has much in common with the modern notion of 'stroke'. Since I am a retired neurologist with an interest in the history of medicine and since in this past career my research has been targeted on the diagnosis and treatment of stroke,[2] it is not surprising that I have chosen to study the early history of this condition.

From apoplexy to stroke

Apoplexy is a term derived from ancient Greek (apoplêxia) and indicates a state of having been dumbstruck or made senseless.[3] The condition is mentioned in the Hippocratic writings, the oldest known source of the notion that human disease does not represent a divine intercession but a natural occurrence, which can be rationally understood and modified.[4] In the book 'Aphorisms' (probably 4th century BCE) one finds the statement "It is impossible to relieve a violent apoplexy and not easy to relieve a mild one."[5] Today, a popular dictionary defines apoplexy as "A sudden loss of consciousness, voluntary movement, and sensation caused by blockage or rupture of a brain artery; a stroke."[6] Between these two citations lies a period of some 2500 years. During this time the definition of apoplexy, like that of many other kinds of disease, has gone through at least three phases of development.

In the first phase the definition of the disease, in this case apoplexy, becomes more specific. After all, it is still a rather broad characterisation to state that, as the aphorism goes, apoplexy strikes suddenly and can result in either death or, in most other cases, in some sort of permanent incapacity. Gradually, in medical circles and subsequently in society, an agreement emerged on a set of clinical phenomena that allows recognition of the disease; at the same time these criteria provide distinction from other diseases that share some but not all of these characteristics. This process merely represents a temporary convention, which the American historian of medicine Rosenberg has called 'framing'.[7] At the present time some diseases are still in this phase. An example is migraine; international committees have drawn up a list of criteria; from time to time these are revised, but there is no litmus test for the diagnosis, let alone a cause. For apoplexy, as I will outline below in more detail, such diagnostic criteria were developed as early as in the 2nd century CE; importantly, they have remained largely valid until well into the 18th century.

The second phase in the 'life cycle' of apoplexy and many other diseases is characterised by the search for causes. 'Cause' is a contentious term; here I use it in the sense of visible changes in organs, corresponding with the clinical features. There has always been general agreement on the brain as the site where the disease 'apoplexy' occurs, but what went actually wrong there remained a controversial issue for a long time. Initially

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2 van der Worp and van Gijn (2007), 'Acute Ischemic Stroke'; van Gijn, et al. (2007), 'Subarachnoid haemorrhage'.

3 Muller and Thiel (1954), *Grieks-Nederlands*, 109.

4 Jouanna (1999), *Hippocrates*, 181-209.

5 Littré, ed. (1839-1861), *Oeuvres Complètes d'Hippocrate,* vol. IV, 482 (aphorism II:42).

6 Fowler, et al. (1990), *Current Oxford Dictionary*, 50.

7 "In some ways disease does not exist until we agree that it does, by perceiving, naming and responding to it." Rosenberg (1992), 'Framing Disease', xiii.

humoural theories dominated, postulating excess of some body fluids over others. In the middle of the 17th century rupture of brain arteries was convincingly identified as a possible cause of apoplexy, in the first quarter of the 19th century occlusion of brain arteries as another. Subcategories followed: different ruptures, different occlusions, both of veins as well as of arteries.

The multiplicity of causes prompted the third phase, in which the 'frame' for making the diagnosis gradually shifted from the clinical features to the cause, the pathophysiological event, for example 'ruptured arterial aneurysm' or 'venous thrombosis'. The umbrella term 'apoplexy', or rather a vernacular form ('stroke', 'Schlaganfall', 'coup de sang', 'beroerte') lingers on among the general public or serves to indicate a medical sub-discipline (the 'stroke unit' in a hospital). Nowadays the clinical features that used to constitute the core criteria of apoplexy do no longer apply; some categories of cerebrovascular disease contain symptoms or signs that were not included in the traditional set, or conversely, they lack elements that were once thought essential, for example complete loss of sensation.

A history of ideas

The history of medicine abounds in social and cultural aspects; one needs to think only of syphilis, malaria, rickets or hysteria. In contrast, the notion of apoplexy does not resonate in social or cultural history. The disease has always struck at random; it does not occur in clusters or even epidemics, and without distinguishing between men and women, or between the rich and the poor. In the 16th century apoplexy was not as common as fevers but not as rare as cancer; a physician might encounter scores of patients in his lifetime.[8] The disease has just been there throughout the centuries, hitting isolated individuals instead of communities. Stroke still fails to cause a broad stir in society, unless the victim is a celebrity such as president Roosevelt, who died at the age of 63 from a brain haemorrhage while he was sitting for a portrait.[9]

So I announce without bashfulness but with conviction that the following history of apoplexy is a 'history of ideas', a history of what physicians thought of its nature and its causes, "a diachronic narrative".

A history with gaps and bias

Several years ago, when I became involved in writing a textbook about stroke with several colleagues from the U.K., I was happy to write an introductory chapter about the history of cerebrovascular disease.[10] In the course of its three subsequent editions I began to feel increasingly uneasy about this text, because I had been unable to consult most primary sources; the reasons were lack of time and loss of the ability to read Latin. Once both these obstacles had been removed and I had started reading and translating texts from the 16th and 17th century, I discovered that not only my own chapter but also most of the other literature about apoplexy left much to be desired.

Of course compendia on the history of medicine can just scratch the surface with regard to any subject, while journal articles can only deal with limited aspects. But I found

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8 Forestus (1653 [1590]), *Observationes et Curationes, volume X*, 505-533.

9 Bruenn (1970), 'Illness and death of F.D. Roosevelt', 590. It will forever remain an unsolved question whether the partition of Europe by the iron curtain would have been different if adequate treatment for high blood pressure had been possible at the time.

10 van Gijn (2007), 'Development of knowledge about cerebrovascular disease'.

that also other book sections, for instance a fat volume on the history of neurology,[11] and even a monograph on the history of stroke,[12] all suffered from three deficits, in different degrees of severity. The first problem is incompleteness; several interesting theories and authors had been completely passed over. This defect overlaps with the second problem: presentism, a notorious trap into which many physician-historians become entangled. It is reverse historiography: to look back into the past from the point of view of the present leads to selection of recognisable landmarks, with neglect of the context to which the 'landmarks' belong, and creates an illusion of orderly progression, with a triumphal ending at the level of knowledge at the time of writing. The third problem is lack of originality; secondary sources mostly lean upon one another – a kind of whispering game in which the original information may well become distorted. So I started from scratch.

[11] Storey and Pols (2010), 'History of cerebrovascular disease'.
[12] Fields and Lemak (1989), *A History of Stroke*.

Chapter 1

INTRODUCTION

Historiographical approach

Search strategy and translations

In this chapter I will explain the approach I have chosen in analysing the early history of ideas physicians had about the causes of apoplexy and of how these have changed: the period I studied and the research question. I finish by setting out my strategy in finding sources.

Historiographical approach

In order to ensure that a story like this constitutes 'research', even if it contains many elements that have not been told before, an analytical tool is required in order to furnish coherence and understanding to the sequence of events. But at first it needs some limitation in time.

The period of study

I decided to begin my search not in Greek antiquity but around 1550 CE. Instead of choosing to perform an exegesis of ancient texts and, if at all possible, to try and synthesize the scattered fragments into a coherent theory, I begin the story with the manner in which European physicians interpreted the Greek tradition, once the relevant texts had again surfaced and become available in complete form. To put it bluntly, European medicine started in 1550 CE where Greek medicine had left off in 200 CE.

I chose 1700 as the end of the period of study. The era between 1550 and 1700 coincides – not by chance – with important developments in the history of science in general. The natural world, traditionally conceptualised in abstract terms, came to be described in materialistic or even atomistic terms, through application of mathematical principles, mechanical notions or experimental methods; purpose as a guiding principle was replaced by necessity.[13] For this reason the era has often been called that of the 'scientific revolution', a historiographic notion developed in the 1930s.[14] Although this periodization has not escaped criticism,[15] or at least qualification,[16] it is not my purpose to enter the fray from the point of view of medicine but rather to regard these larger changes as the intellectual environment with which medicine interacted. Some have commented that life sciences do not fit in this mould of mathematization and mechanistic thinking.[17] On the other hand the Scientific Revolution has been recently represented as the convergence of three entirely different methods in acquiring nature knowledge: through philosophical abstractions, or in a mathematical fashion, or by systematic observation and fact-finding.[18] It is this third mode of obtaining nature knowledge that applies to biology and medicine.

I have cut the main body of my narrative in two, with a separate chapter for each half of the stretch of 150 years. The reason is that in the middle of the period between 1550 and 1700 William Harvey proposed the theory of the circulation of blood. This theory would eventually prove a turning point in the ideas about apoplexy, even though Harvey's model remained controversial for decades. Whereas movements of blood hardly played a role in the explanation of apoplexy before that time, the gradually accruing number of 'believers' in the circulation theory saw it as an essential factor in understanding what was going on in the brain to cause this disease.

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[13] Dijksterhuis (1950), *Mechanisering*.

[14] Cohen (2010), *How Modern Science came into the World*, xvii.

[15] Park and Daston (2006), 'The age of the new', 13.

[16] Cunningham and Williams (1993), 'De-centring the big Picture', 413-414.

[17] *ibidem,* 413.

[18] Cohen (2010), *How Modern Science came into the World*, 113-141; Cook (2007), *Matters of Exchange*, 16-17.

Research question
The body of knowledge available to European physicians in 1550 contained a mixture of much speculation, some observations and, occasionally, an experiment. In 1709, at end of the period I studied, Boerhaave, at the time 40 years old and professor of medical botany at the University of Leiden, published the first edition of his famous 'aphorisms', following the example of Hippocrates. In the section on apoplexy, looking back on the variety of causes of apoplexy he had just listed, he wrote:

> It is anatomical inspection of the cadavers of [patients] who succumbed to apoplexy that has taught [us] these causes, as well as the historical observation of the [events] that can be observed during the treatment of these patients.[19]

Broadly, my research question revolves around the observations Boerhaave alludes to. Undoubtedly, inspection and observation were the only methods available to physicians in their search for the causes of apoplexy; indeed no telescopes, microscopes or other instruments could assist them. But it still needs to be investigated whether new ideas were indeed always driven by observations, and, if so, how accurately and true-to-nature the observations were reported.

So, because I wished to find out how the understanding of apoplexy changed between 1550 and 1700, I studied and translated relevant printed treatises in this period in order to analyse the manner in which physicians used to report their observations. Was the report detailed and untainted by conclusions that might eventually be drawn from them, or was the wording more global and interpretative? And, if the observers drew theoretical conclusions from what they saw, were these conclusions justified by the observations or were they still speculative, wholly or in part? In the process of passing judgements about the manner in which past actors recorded their observations I have aimed at striking a balance between 'embeddedness' and 'distance', to paraphrase Rosenberg's plea for integration between 'cognition' and 'context' and between 'internalist' and 'externalist' approaches.[20]

Of course the distinction between observation and interpretation is not sharp,[21] not even in particle physics.[22] Seeing is always to some extent believing; visual impressions are often selective or fraught with meaning. Medicine is no exception.[23] I have avoided the term 'objective', not only because it is a modern notion but also because it evokes the false connotation that subjectivity can be excluded.[24]

Search strategy and translations

The first question was how to make an appropriate selection among the multitude of physicians who produced smaller or larger sections of printed text about apoplexy in the second part of the 16th and the entire 17th century. I decided to use different methods for each half of this era.

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19 Boerhaave (1709), *Aphorismi de cognoscendis et curandis morbis*, 252-253.
20 Rosenberg (1988), 'Woods or trees?'
21 Hanson (1958), *Patterns of Discovery*, 4-30.
22 Pickering (1984), 'Against putting the phenomena first'.
23 van Gijn and Bonke (1977), 'Interpretation of plantar reflexes'.
24 Daston and Galison (2007), *Objectivity*. Others maintain that the term can nevertheless be applied to the study of past periods, in the sense of a detailed acquaintance with objects, as synonym of 'truth-to-nature' (Cook (2007), *Matters of Exchange*, 17-20).

Choosing authors from the period 1550-1625

There are no monographs on apoplexy from this period, but I included one book published in 1629, since its contents are entirely devoid of any reference to Harvey's theory of the circulation of blood, which had appeared a year before. Apart from this source, every compendium of diseases – and there were many – spent at least a few lines on the subject. I reasoned that I might detect the most original and important writers among the many medical authors in this period by a doxographic method, that is, by tabulating citations by physicians of a few generations later. So I started this project by reading the first two monographs about apoplexy that appeared in roughly the first half of the 17th century, including the one I just referred to, published in 1629.[25] These two books together contained citations referring to the work of 149 different authors. From this group of cited authors I subsequently selected those born between 1400 and 1570, in order to exclude ancient as well as contemporary authors. The results appear in table 1.

cited author	*year of birth-death*	*number of times cited by*		
		Nymann	***Wepfer***	***total***
Felix Platter	1536-1614	9	10	19
Andreas Vesalius	1514-1564	3	15	18
Jean Fernel	1497-1558	9	5	14
Pieter van Foreest	1521-1579	11	3	14
Gaspard Bauhin	1560-1524	5	8	13
Costanzo Varolio	1543-1575	8	4	12
Wilhelm Fabry	1560-1634	5	5	10
Adrianus Spigelius	1539-1619	3	5	8
Paracelsus	1493-1541	8	-	8
Pietro Salio Diverso	fl. 1580	1	6	7
Ercole Sassonia	1551-1607	3	3	6
Charles le Pois (Piso)	1563-1633	-	6	6
Alessandro Massaria	1510-1598	3	2	5
Girolamo Mercuriale	1530-1606	3	2	5

Table 1. *Citation frequency of authors born between 1400 and 1570 in the monographs on apoplexy by Gregor Nymann (1629) and Johann Jakob Wepfer (1658).*

The table shows the 14 most cited authors (almost invariably with positive connotations) by the two monograph authors together, from a total of 75 authors born between 1300 and 1570. This selection contains all authors cited by both sources. I decided to discuss at least the first seven authors of the list for the present study and to include texts of the remaining authors only in case they would turn out to offer points of view not mentioned before.

Choosing authors from the period 1625-1700

In the 17th century the first monograph on apoplexy to take account of the new theory of the circulation of blood appeared in 1658.[26] This was followed by several other books about

[25] Nymannus (1629), *Tractatus de Apoplexia*; Wepfer (1658), *Observationes Anatomicae*

[26] Wepfer (1658), *Observationes Anatomicae*.

apoplexy and brain disease, which commented on each other and on earlier publications.[27] So it is this *ensemble* of monographs published after 1650, written by practising physicians as well as by university teachers, that forms my main source for the second period of 75 years. I will refer to other publications cited by the 'top authors' if these seem relevant.

Hippocrates, Galen and other writers from antiquity
At the end of the following chapter there is a section on the definition of apoplexy where I refer a few times to modern editions of Hippocrates and Galen, the Greek text having been translated in English or Latin. In later chapters however, where I discuss views of 16th- and 17th-century physicians in which they seek support from their predecessors in antiquity, I will not return to these original sources, even though the respective authors may indicate them. Instead, I will present the interpretation of the later generations of physicians, without attempts to add my personal interpretation of ancient sources.

Exclusions
The diagnosis of apoplexy has often been made not only in patients whose illness developed unexpectedly, by factors occurring inside the body, but also in patients who suffered from external causes of brain damage, such as bullet wounds, blows or falls from height, after which they became senseless and motionless as a result, but without instantaneous death. I have largely omitted this category of patients from my account, even though at the time the clinical features were thought to justify a diagnosis of an 'apoplectic state'. After all, the subject of this thesis is how physicians thought about hidden causes of apoplexy, defined as a spontaneous event; external causes are obvious and therefore hardly enlightening.

A further limitation is that I will be very brief on treatment. Even though ideas about causes of apoplexy changed in the course of time, therapeutic measures remained fairly stable until about 1800. Also they consisted for a large part in medical recipes based on theories about the effects of herbs and other plants, a subject far removed from the issues that are central to this study.

Finally, the study is limited to Europe, with the exception of the role Byzantine and Arab physicians had on the European medical tradition in the period between roughly 600 and 1400, as mentioned before. I must remain silent on all other parts of the world.

Translations
Most if not all medical texts discussed in the following sections have been written in Latin. The translations of the quoted texts are all mine, unless indicated otherwise. I pride myself on a proper education in Latin language and culture, but I cannot base it on life-long experience. On the other hand, not all writers I encountered appeared to have had excellent schooling or aptitude, while medical texts often contain ambiguous words such as *ratio, res, or corpus*. All this implies that I do by no means regard these translations as definitive.

Digital appendix
This thesis has an appendix in the form of a removable digital memory card. This appendix contains the original Latin texts I have used, side by side with my translations. Some texts have been completely translated, others only partly. An index of the texts on the memory card is appended to this thesis.

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[27] Willis (1672), *De Anima Brutorum*; Bayle (1677), *Tractatus de Apoplexia*; Cortnumm (1677), *De morbo attonito*.

Chapter 2

MEDICINE IN THE 16TH CENTURY

Doctors

Medical education

Autopsy: the anatomy of disease

Communication between physicians

The purpose of this chapter is to sketch the state of medical training and practice at the outset of my study period. All medical authors who will appear in this story received their education at one or more European universities; they would have learned Latin in secondary school, while most universities required courses in natural philosophy as a prelude to a professional education in medicine. The one and only task of a university was teaching. 'Research' was non-existent, not only as an organised activity or practice but also as a goal at large, at least until the 17th century. Some universities (for example Padua and Leiden) had loose affiliations with a city hospital, but, again, the inpatients served only for teaching. Of course hospitalised patients received not only care but also treatment, in university towns and elsewhere. At their homes they could consult academic physicians or other healers.

Doctors

Physicians with university training were few and far between in the 16th century. They tended to be concentrated in the larger cities but were few in number, while unlicensed practitioners predominated in the countryside.[28] Some academics had an appointment as town physician and were supposed to care for the population at large, at least for indigent townspeople and travellers; often they were also responsible for matters affecting the entire community, such as epidemics of contagious disease. But even in towns most families were too poor to allow themselves a university-trained doctor; often they had to take recourse to medical self-help literature – if they could read – and to home remedies. Bloodletting, for instance, was quite common even for prophylactic purposes. The vein cutter would often be a barber-surgeon, who might also practice non-surgical aspects of medicine and who provided of a large part of overall medical care well into the 19th century. Finally there would be apothecaries, distillers and a large array of faith healers, astrologers, soothsayers and healers of both sexes who all offered their services.[29]

Medical education

In the first half of the 16th century, the most prestigious universities for medical education on the European continent for students from Northern Europe were Paris, Montpellier, and especially the Northern Italian cities of Bologna and Padua. In the Iberian Peninsula, most universities specialised in the teaching of law, in order to train future civil servants; Spanish and Portuguese students also went to Montpellier, Parma, Ferrara, Siena and Pisa.[30] Oxford and Cambridge were modelled early in the century after the universities of Northern Italy; they might offer university degrees in medicine, but hardly provided opportunities for practical experience.[31] Louvain did have a medical faculty, but the standard of medical teaching was not very high in the 16th century.[32] This is probably one of the reasons that Andreas Vesalius from Brussels (1514-1564) as well as Pieter van Foreest (1521-1597), from Alkmaar (in the Northern Netherlands), studied only liberal arts in Louvain and subsequently went elsewhere to continue their study of medicine.

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[28] Pelling and Webster (1979), 'Medical Practitioners'.
[29] Stolberg (2011), *Illness*, 59-62.
[30] Arrizabalaga (2009), 'Spanish Students', 93-126; Farelo (2009), 'Portuguese Students', 127-147.
[31] Pelling and Webster (1979), 'Medical Practitioners', 167-173; Nutton and Porter (1995), 'Introduction'.
[32] Santing (2009), 'van Foreest', 152-153.

Traveling around different universities, though common in the 16th and well into the 17th century, was a matter of wealth. Van Foreest, for example, was from a patrician family; after the first few years in Louvain he could continue his studies at the universities of Paris, Bologna and Padua, with intermissions in Rome and other Italian towns of cultural interest.[33] Jean Fernel (1497-1558), on the other hand, came from a much more modest background; he stayed in Paris during his entire university training and had to pay largely his own way.

An essential feature of medical teaching, and of education in general, was the availability of printed books, after Gutenberg's invention around 1450. In the course of the following century the number of printed medical titles increased by a factor of one hundred, while the number of copies per title soared exponentially.[34] Libraries rapidly expanded, not only in university institutions, but also in private homes. In Cambridge for example, inventories show that in the second half of the 16th century physicians mostly owned between 50 and 100 books, a professor even several hundreds. Even laypersons might possess scores of medical books.[35]

Students had a large influence on the culture as well as on the management of the universities; often they paid fees directly to the professor rather than to the university and so voted with their feet about the quality of teaching. In Bologna and Padua a large proportion of students was foreign; they were organised into *nationes*, according to their region of origin. In the second half of the 16th century Padua became the most popular venue for students from abroad, either in the course of a more extensive *peregrinatio medica,*[36] or to finish one's education by obtaining a doctorate.

As will become clear in the course of this story, many developments in medicine, including the subject of apoplexy, have taken place at the universities in Northern Italy. Also many protagonists who will appear in this thesis studied for one or more years in Bologna or, most often, Padua. Students often retained vivid memories of lectures and practical experiences and recounted these at home. It is therefore appropriate to choose the example of Padua for a closer look at medical education in the 16th century.

Padua

The university of Padua dates from the first half of the 13th century, when students of law from Bologna came over in search of teachers who were less obsequious to instructions from the Vatican. The family Da Carrara dominated the city for most of the 14th century, but after 1405 Padua came under the reign of the Republic of Venice. This ensured a liberal political and religious climate, owing to the bustling Venetian merchants' frequent contacts with other civilisations in the eastern Mediterranean.[37] Sometimes the freedom of Venetian speech gave even rise to complaints, as exemplified by Francisco Petrarca (1304-1374), who lived in Venice for some time.[38] In the 15th and early 16th century humanism flourished in Venice; many printers established themselves in the Republic, while teachers from far and wide were invited to teach at Padua. Meanwhile Northern Italy was often a battleground between the Venetian Republic, the Pope and the King of France, with shifting alliances.

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33 *ibidem,* 154-159.

34 Jones (1995), 'Reading Medicine', 155-156; Nutton (2005), 'Printing and Medicine', 421-442.

35 Jones (1995), 'Reading Medicine', 164.

36 Cunningham (2009), 'Peregrinatio Medica'; de Ridder-Symoens (2009), 'Mobility of Medical Students', 47-89; Frank-van Westrienen (1983), *De Groote Tour*.

37 Gallo (2001), 'L'Età Medioevale', 1-33.

38 Petrarca (2001), 'Invectiva', 344.

***Figure 1**. The university of Padua in 1654. Engraving by Giacomo Filippo Tomasselli.*

It was for several reasons that medical students were attracted to Padua, from Italy as well as from abroad (figure 1). Its medical faculty not only had a great reputation but it was also large, like that in Bologna; physicians in Italy were relatively numerous and they were distributed geographically as well as across social classes.[39] Moreover, for each chair there would often be at least five professors (First and Second Ordinary and First, Second and Third Extraordinary), at least for the three main subjects: theoretical medicine, practical medicine and natural philosophy. Theoretical medicine consisted of general introductions to health and disease, based on ancient texts, especially Hippocrates' *Aphorisms* and Galen's *Ars Medica*; the professor of practical medicine would present a survey of the different diseases. Native citizens of Padua were not eligible for a First Ordinary professorship in any subject; if a vacancy occurred, the Senate of the Republic of Venice (*La Serenissima*) made efforts to attract the candidate with the best reputation from abroad.[40]

The fame of the teachers in Padua greatly contributed to the large number of its students. Importantly, there were no barriers with regard to religious conviction. Protestant students from Northern Europe as well as Jewish students were welcome, despite attempts to bar them by forces of the counterreformation such as papal decrees and the Jesuit College.[41] Finally, professors often had a practice in town and would take a group of students in tow when they visited their patients in hospital or at home, quite apart from formal lectures. The students were taught to feel the pulse, inspect the urine and select the

[39] Bylebyl (1979), 'The School of Padua', 336.
[40] *ibidem,* 343.
[41] Farelo (2009), 'Portuguese Students', 136; Del Negro (2001), 'L'Età moderne', 48-54.

proper recipe from the available array of plant concoctions, the *materia medica*. Most famous – though not the first - in this tradition was Giovan Batista de Monte (*Montanus*).[42]

Surgery never ceased to be an academic discipline in Northern Italy, unlike most arrangements elsewhere. In Padua it was taught by a lecturer, who had the additional task of anatomical instruction by means of dissection; in the first half of the century dissections occurred gradually more often, instead of being an annual event.[43] Important professors for these subjects were Nicolò Massa and especially Andreas Vesalius (1514-1564), who taught from 1537 to 1544;[44] Vesalius' rapid fame is based on the accuracy and artistic appeal of the illustrations in his anatomical atlas *Humani Corporis Fabrica* (1543) and on the frank manner in which he discussed inaccuracies in the writings of Galen. After his departure, the academic status of anatomy had risen and surpassed that of surgery.[45] His successors Realdo Colombo and Gabriele Falloppia (*Falloppius*) concentrated on descriptive anatomy, as Vesalius had done. On the other hand, Girolamo Fabrici d'Aquapendente or *Fabricius* (1533-1599), in 1559 appointed to a First Ordinary chair of anatomy and surgery, shifted the emphasis of his teaching to the relationship between anatomy and natural philosophy, in other words the relation between structure and function;[46] in addition he managed the construction of an anatomical theatre that would become famous and that is still extant.

'Research'

In the first half of the 16th century texts of ancient medicine had been recovered to a far greater extent than before, when only summaries with Arab interpretations had been available. This change caused young physicians like Jean Fernel to groan that he had to begin studying all over again.[47] Understandably, in the next few decades attempts by physicians to build a common knowledge base revolved in the first place around the proper interpretation of these ancients texts, since these were often ambiguous or even contradictory.

As we shall see, it was especially in the field of anatomy and especially in the younger generation that it is possible for us to discern some awareness that wisdom did not only reside in texts. The 28-year-old Andreas Vesalius was not only a gifted anatomist who managed to engage brilliant artists for his seminal book of 1543, but also an unconventional if not revolutionary thinker:

> I am well aware how physicians (much more than the followers of Aristotle) tend to become upset when in the course of a single dissection Galen has erred more than two hundred times from a true description of the harmony of human body parts and of their purpose and function; in panic they scrutinise the dissected parts, in their utmost zeal to defend him.[48]

Some thirty years later, the 29-year-old Costanzo Varolio in Bologna, following in Vesalius' footsteps, went even further:

> I think this knowledge will never attain such a level that nothing is left to find for posterity.[49]

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42 Bylebyl (1979), 'The School of Padua', 347-349.
43 *ibidem,* 342.
44 Ongaro (2001), 'Medicina',163-171.
45 Bylebyl (1979), 'The School of Padua', 358-362; Klestinec (2009), 'Education at Padua', 196-206.
46 Cunningham (1985), 'Fabricius', 201-207.
47 Plantius (Plancy) (1607), 'Vita Fernelii', *2.
48 Vesalius (1543), *Fabrica*, dedication to Emperor Charles V, 4.
49 Varolio (1573), *De Nervis Opticis*, 1v.

But Vesalius and Varolio were exceptions. 'Research' was definitely not on the agenda of universities, hospitals, aristocratic courts or medical societies.

Autopsy: the anatomy of disease

Opening of the human body after death is fraught with public apprehensions and taboos among the general population. In the eyes of the public there was – and perhaps is – no great distinction, with regard to the disgrace of the procedure and the risk of being denied a proper burial, between on the one hand the practice of being 'anatomized' for the instruction of medical students, as could be the lot of criminals undergoing capital punishment, and on the other hand the search of physicians for causes of disease and death in the bodies of patients they had been trying to save. For example, a female character in a well-known 19th-century British novel distrusts the motivation of her doctor:

> 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.[50]

But in fact there were vast differences between these two procedures. These have to do with the minds and aims of doctors, with the locations where dissection took place, anatomical theatre or mortuary, improvised or not, and with the very methods of the investigations. It is therefore surprising that some historians make little distinction between these two kinds of dissection,[51] historians of medicine not excluded.[52] In this section I will only discuss the post mortem investigation, or autopsy as it is commonly called, in the sense of an investigative tool for the reconstruction of the causes of disease.

In ancient medicine, explanations of disease revolved around the proportions of fluids in the body, particularly the four main humours observed (blood, phlegm, bile) or hypothesized (black bile). Apart from embalming, almost always carried out by servants, medical dissection of the human body after death was performed only in Alexandria, probably only in the third century BCE; the procedure was considered taboo in all other ancient periods, including the time of Galen.[53] The Alexandrian physician Erasistratus (c. 310-250 BCE) was therefore exceptional in that he left a report about the state of solid organs.[54]

In the 13th and 14th century dissection rarely occurred in Northern Italy, mostly for legal reasons. The attitude of the Catholic Church was often negative, but the objections were based on humanitarian and aesthetic rather than on religious grounds.[55] Nevertheless in the course of the 14th century dissections were gradually introduced at medical schools, as the first anatomical treatise of Mondino dei Luzzi (1316) testifies. It seems that clerical opposition was less if the purpose of dissection was scientific instead of didactic.[56]

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50 Eliot (2011 [1872]), *Middlemarch*, 442-443 (chapter 45).
51 Sawday (1995), *The Body Emblazoned*.
52 Cunningham (2010), *The Anatomist Anatomis'd*, 17-82.
53 von Staden (1992), 'Human dissection in ancient Greece'.
54 King and Meehan (1973), 'A history of the autopsy', 517-518.
55 *ibidem,* 519-521.
56 Carlino (1994), *Books of the Body*, 182-186.

As long as medical knowledge was dominated and limited by Galenic texts, there was little inducement towards the procedure of dissection, as it could have little effect on medical practice; exceptions in the late 15th and early 16th century were Benedetti, Benivieni and Massa.[57] In the second half of the 16th century physicians became more often inquisitive and started performing post-mortem dissections if they obtained permission — or furtively if this was denied, as the example of Platter (page 53) shows.

In the 17th century the collection of facts *per se*, new ways of knowing without connection to reasoned causes, in short 'curiosity', became increasingly common.[58] Physicians were no exception. At the close of the 17th century Théophile Bonet (1620-1689), a physician in Geneva who was forced to give up his practice because of increasing deafness,[59] made an important contribution to medicine by collecting and compiling all autopsy reports he could find; eventually he published the results in two folio volumes, the *Sepulchretum* ('Graveyard').[60] The books contain over 3000 records, from approximately 450 authors. The case reports range in length from a few lines to a few pages; after each report, or sometimes a pair of related cases, Bonet wrote a comment (*scholium*).

Under the heading 'apoplexy' Bonet arranged 67 case histories; in many of these the diagnosis was not in agreement with the usual phenomenological criteria I will outline in the next chapter, for different reasons: external causes instead of a spontaneous onset, or sudden death, or an 'apoplectic state' in the course of a protracted illness, or only indirect information such as hearsay, or a general statement, or failure to examine the brain as part of the dissection. Apart from all such atypical events, twenty case histories remained; only two of these dated from the 16th century. In eleven of the twenty stories the clinical information was at least compatible with the diagnosis of apoplexy, but not detailed enough to allow a judgement whether the clinical phenomena in fact corresponded with the criteria that were commonly applied at the time. So a mere nine case histories remain in which detailed clinical as well as pathological descriptions are available. As a matter of course, I will discuss at least these nine observations in the course of this thesis.

Communication between physicians

Since my subject is the development of physicians' ideas with regard to apoplexy, this prompts the question how they exchanged their views. The global answer is that the means of communication were travel and reading, while mastery of the Latin language united learned communities far apart. All protagonists in my story were writers of books and letters. The books might be general textbooks covering the whole of medicine, such as compendia from different sources, *Medica Practica*,[61] organised from head to heel, or, a bit later, Fernel's *Medicina*, in which the approach was according to symptoms.[62] Less common were monographs, such as Pratensis' book about diseases of the nervous system.[63]

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57 *ibidem,* 191-193.

58 Cook (2006), 'Medicine', 16-17.

59 Irons (1942), 'Théophile Bonet, 1620-1689'.

60 Bonetus (1679), *Sepulchretum*. After the first edition in 1679, Jean-Jacques Manget prepared in 1700 a second and expanded edition, in three volumes (published in Leiden).

61 Siraisi (2008), 'Girolamo Mercuriale'; Siraisi (1985), 'Avicenna'.

62 Fernelius (1554), *Medicina*.

63 Pratensis (1549), *De Cerebri Morbis*.

Letters constituted an important form of communication between physicians. Such a letter might be directly addressed to another physician, as is the case with the correspondence between Varolius and Mercurialis (see chapter 4), or it might be sent to a colleague who acted as editor of a compilation of letters, with a view to publication; such compilations became more common after 1550, for example the *Centuriae* of Krato von Krafftheim (medical) or of Wilhelm Fabry (surgical).[64] Another category of publications that became popular in the second half of the 16th century was formed by series of personal observations, mostly from well-known traveling doctors or city physicians: Amatus Lusitanus, Francois Valleriola, Rembert Dodoens and especially Pieter van Foreest, who will prominently appear later in this story.[65] Importantly, all followed Amatus' example of separating the case history from a subsequent theoretical commentary, the so-called *scholia*.[66] Finally, case histories might be culled from published works; an example is the collection of dissections by Bonet I just mentioned, another a selection of notable case histories in general, by Schenck von Grafenberg.[67]

I will not attempt a systematic review of the medical networks with regard to apoplexy, if these exists at all, but I will indicate the source of each new idea as it turns up.

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64 Siraisi (2013), *Epistolary Medicine*, 1-12; Pomata (2010), 'Sharing Cases'.
65 Forestus (1653 [1590]), *Observationes et Curationes,* volume X.
66 Pomata (2011), 'Observation Rising', 54-60.
67 Schenck von Grafenberg (1609), *Observationum*.

Chapter 3

IDEAS ABOUT NATURE, THE BRAIN AND APOPLEXY AROUND 1550

Nature

The brain

Apoplexy

My intention in this chapter is to present an outline of the ideas that were more or less generally adhered to in the circles of academic physicians in the middle of the 16th century about the structure of matter in general and that of living creatures. Next follows a description of academic opinions about the brain at that time in history, from a functional as well as a structural point of view. I close with a résumé of the criteria for the diagnosis of apoplexy in the 16th and 17th century.

Nature

The structure of matter

To illustrate ideas about the structure of matter in general I chose, perhaps somewhat surprisingly, one of the physicians who were most often cited on the subject of apoplexy in the first two 17th-century monographs on the subject. His name is Jean Fernel (1497-1558; see box).[68] He fits the purpose not only with regard to publication date (1554), but especially because the book in question, *Medicina,* starts with a separate part on the basic principles of matter as well as the structure and internal functions of living creatures. This first of the book's three parts is entitled *Physiologia*, a newly coined term, literally meaning 'Laws of Nature'; the new name has withstood the test of time. Fernel's *Physiologia* was the first treatise of its kind after Galen's 'On the function of Body Parts' (*De Usu Partium*). An initial version had appeared twelve years before, with a different title.[69] So it is to Fernel that I turn for an impression of how in the middle of the 16th century physicians and philosophers – the distinction was often not sharp in those times – interpreted the world around them and the bodies of their patients.

With its 250 quarto pages *Physiologia* is as much a philosophical treatise as an introduction to the knowledge of diseases and their treatment. Fernel writes in great detail, often with several of arguments for single points of view. In the following sections I will attempt to summarise his reasoning and also to limit the story to issues most relevant to the subject of apoplexy.[70] The authorities on whom Fernel leans in this treatise are Hippocrates, Aristotle and Galen. Contemporary writers are mentioned only in a categorical sense, as 'modernists' (*iuvenes* or *neoterici*), while the Arab authors Avicenna (980-1037) and

Jean Fernel (1497-1558)

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

For the next five years Fernel studied Plato, Aristotle and Cicero on his own, while developing an interest in mathematics. In order to enter a professional career he finally chose to study medicine, while he had to provide for his own living by teaching, since his father had to support the other children as well. In 1530 he graduated in medicine and obtained a licence to practice; in the mean time he had published three folio volumes on mathemat-ical and astronomical subjects. Soon afterwards he married and had to give precedence to his medical practice. He continued teaching until in 1550 his practice became too large; probably the lectures were private, because he was never officially appointed and the relations with his colleagues at the medical faculty were rather strained. In 1542 he was appointed physician to the Dauphin; when the latter became King Henri II in 1547, he excused himself from this function until ten years later.

68 Sherrington (1946), *Jean Fernel*.
69 Fernelius (1542), *De naturali parte medicinae*.
70 Fernelius (1554), *Medicina (Physiologia)*, 70-121.

Averroes (1126-1198) receive only derogatory comments because of their errors and distortions, in keeping with the newly restored guiding light of ‘pure Greek science’.[71] Fernel characterised the cultural and scientific reorientation that came to be called ‘Renaissance’ in the 19th century as a ‘rebirth’, with the following words: “These disciplines and arts have clearly come to life again, after having been buried, or rather extinct and lifeless, for almost twelve hundred years.”[72] As a means of diversion Fernel sprinkled his text with lines from *De Rerum Natura*, a famous treatise written in hexametric verses by the Roman poet Lucretius (99-55 BCE), who was inspired by the atomistic world view of the philosopher Epicurus (341-270 BCE).

Since it is unthinkable that nature consists of only a single substance – otherwise there would be no interactions, the argument goes – it must be made up of combinations of elements. There are four of these: fire, air, water and earth. This theoretical construction, without any empirical basis, was first proposed by Empedocles (c. 492-c. 432 BCE) and elaborated by Aristotle (384-322 BCE). At first sight this system strikes readers in the 21st century as primitive and antiquated. On the other hand the theory was largely coherent and not in obvious conflict with day-to-day observations at the time. Simplicity in science is always attractive but often elusive; an example from our own time is the growing awareness that the popular notion of DNA, defined by the sequence of four ‘letter’ (nucleic acids), as the ‘blueprint’ of an organism represents a gross underestimation of biological complexity.

Each of the four elements is supposed to possess specific qualities – I use the present tense to bring the ideas a bit closer. These qualities, though important, are properties (‘accidentals’, in Aristotelian terms), not part of intrinsic being (‘essence’) of the element. The properties all relate to the sense of touch, which is regarded as the most important sense organ; heat and cold are directly perceived, while the degree of wetness is derived from the softness of an object. The primary quality represents the extreme of its kind: nothing is hotter than fire, or colder than frozen water, etc. The elements also have secondary qualities, borrowed from one of the other elements, but less intense:

	primary quality	*secondary quality*
fire	heat	dryness
air	wetness	heat
water	cold (if frozen)	wetness
earth	dryness	cold

Each body or object, living or inert, is made up of all four elements.[73] In combining, each element merges with its respective opponent (one cannot help thinking of the analogy with the nucleotide pairs in DNA: adenine matching only with thymine, cytosine only with guanine). With regard to qualities the fusion is complete, the end result being some equilibrium at a given point between hot and cold or between dry and wet. The substances of the elements, however, do not coalesce completely, as Avicenna believed, but are only closely knit together. The substance and the qualities of the elements making up an object are not lost, but remain in hiding, as it were; after death or destruction the object or cadaver decomposes again into its original constituents.

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71 Wear (1995), ‘Early Modern Europe’, 251-155; Siraisi (1985), ‘Avicenna’, 39-41; French (1985), ‘Berengario’, 66-71.

72 Fernelius (1548), *De Abditis Causis*, 2.

73 Aristotle’s theory has other interpretations as well: Dijksterhuis (1950), *Mechanisering*, 220-225.

The body of animals and man

Living bodies are made up of the same four elements as everything else. Growth and repair are regulated by the system of digestion, which breaks down foodstuffs like fish, fruit or grass into its constituent elements and subsequently reconstructs them first into blood and subsequently into flesh or any other body constituent.

An important principle is that of 'temperament', which refers to the proportions in which the four elements are mixed. These proportions differ according to organ, to individual and to species; a perfect equilibrium (*temperies*, or optimal blend) is the exception rather than the rule. Often one or two elements are dominant in the composition. With regard to organs, Fernel catalogues more than twenty body parts according to their position on the axis between dryness and hotness as well between heat and cold, so that one might construct a two-dimensional diagram in which each organ has its place. Skin forms the middle on both axes; the heart is the warmest part apart from spirits (see below), but the spirits have not been classified with regard to wetness; phlegm is the coldest and wettest constituent. The brain is also rather wet and cold, but not extremely so.

The overall temperament of the body is determined not only by the temperament of its constituent body parts, but also by a kind of vital heat that is separate from the intrinsic heat of the four elements; after death this heat dissipates much quicker than can be explained by decomposition of the body into its foundational elements. Finally, age influences temperament in that people tend to become colder after adulthood, while the overall degree of wetness decreases from infancy onwards.

The four main humours in the body are blood, yellow bile, black bile and phlegm. They are all produced in the liver and they all circulate within blood vessels. Regularly there is an excess of one or other of these, so that the superfluous part has to be excreted – each in its separate way. Fernel stresses, in contrast to the interpretation of the Greek heritage by several other writers of his time, that it is important to keep the notion of temperament apart from the proportion of these four fluids: temperament is determined by the proportion of constituent elements, not by those of humours. The humours do not make up the body, but they are contained in it. One can say of a *person* that he is sanguineous, bilious, melancholic or phlegmatic, but not of a temperament, also because the ratio between the four humours is inconstant. On average, there is a gradual change between this ratio in the course of life: infants show a preponderance of blood, children of yellow bile; in adolescence the proportions are in optimal balance, adults have a relative excess of black bile and aged people of phlegm.

The humours, or at least three of them (yellow bile is the exception) have an important role in the explanations physicians of the 16th century used to explain apoplexy, as I will explain later. According to ancient Greek theory, especially Galen, a person's health depends on an optimal balance (*temperamentum*) between these fluids, while a mild imbalance may define a person's constitution as phlegmatic, sanguine, choleric or melancholic. Disease can be the result of severe imbalance, usually precipitated by local factors in the body or external influences.

The brain

The function of the brain

Fernel represents the Galenic model - though without actually mentioning Galen - of the manner in which the brain performs its function in a much more concise fashion than he did in the case of the building blocks of nature. Therefore it is useful to let him speak for himself:

> The portion of the food that is rather pure and more or less like air develops through digestion into a rather subtle component of blood, of a kind that has the appearance of vapour. Then, when it receives the power of the intrinsic spirit of the liver and it is completely imbued with its abundance, it becomes natural spirit; the more the intrinsic, natural power of the liver exceeds its mass, the more [the natural spirit] will stand out from the rest of the blood. Depending on the quantity of this spirit that is carried away together with the blood via the hollow vein and transported to the heart, it is there again improved and refined, almost changed into a kind of air. From the right cavity of the heart it then seeks passage to the left cavity, via common and extremely narrow openings; there it is combined with air drawn via the lungs; it becomes some kind of matter furnished with vital warmth and force and [so] produces the vital spirit that is diffused and carried via the arteries through the entire body. The portion of it that is taken to the base of the brain via the arteries of the neck, mollified for a third time by the twists of the admirable web, is soon transported to the ventricles of the brain via another web, called choroid. There, by means of air drawn in from the nose and [then] refined, it receives improvement and fuel; through [this] force and property the intrinsic spirit of the brain becomes by some kind of conversion the animated spirit, clearly modelled after aether and aptly prepared to perform movement, sensation, in short all mental functions. Thus, if the vapour of blood that has been generated in the liver provides the material and the nourishment, as it were, for the vital spirit and subsequently also for the animated spirit, it should be placed without delay in the first rank of spirits. As much as this differs from vital spirit, the vital spirit differs from the subtlety of the animated spirit; after all, the natural spirit equals vapour, the vital spirit is aerial and the animated spirit aethereal. If we call the vital [form] a spirit, similar to the animated [form], why not in the same way the natural one?[74]

Fernel's plea, at the end of this passage, to use the term 'spirit' also for the raw material provided by the liver goes a bit beyond the descriptions of Galen, who was rather equivocal on this point.[75] I included these sentences not because they help to understand Galen's notions on brain function, but to illustrate the remnants of scholastic preoccupations with terminology that can still be found in writers who regard themselves as moderns.

Let me summarise the model (figure 2). The liver, thought to synthesize blood from digested food, adds a vapour-like component to it, which some prefer to call 'natural spirit'. The second stage takes place in the heart, where 'vital spirit' is formed from the vaporous component of blood by mixing it with air from the lungs, influenced by the innate heat of the heart. In the third and final stage the vital spirit is transported to the ventricles of the brain and upgraded to 'animated spirit', through intrinsic properties of the brain and with some contribution from air inhaled through the nose. The animated spirits perform all the functions of the brain, internally (such as reasoning, imagination, memory) as well as externally by flowing from the brain into the nerves connected to it and giving rise to movement or to external sensations (vision, hearing, feeling, etc.).

The excrements of the brain, Fernel continues, form 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 accepts its coldness before it is 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.[76] I will soon come back on the structures thought to be involved in this excretory transport.

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74 Fernelius (1554), *Medicina* (Physiologia), 120-121.
75 Harris (1973), *The Heart*, 349-351.
76 Fernelius (1554), *Medicina* (Physiologia), 183 and 192.

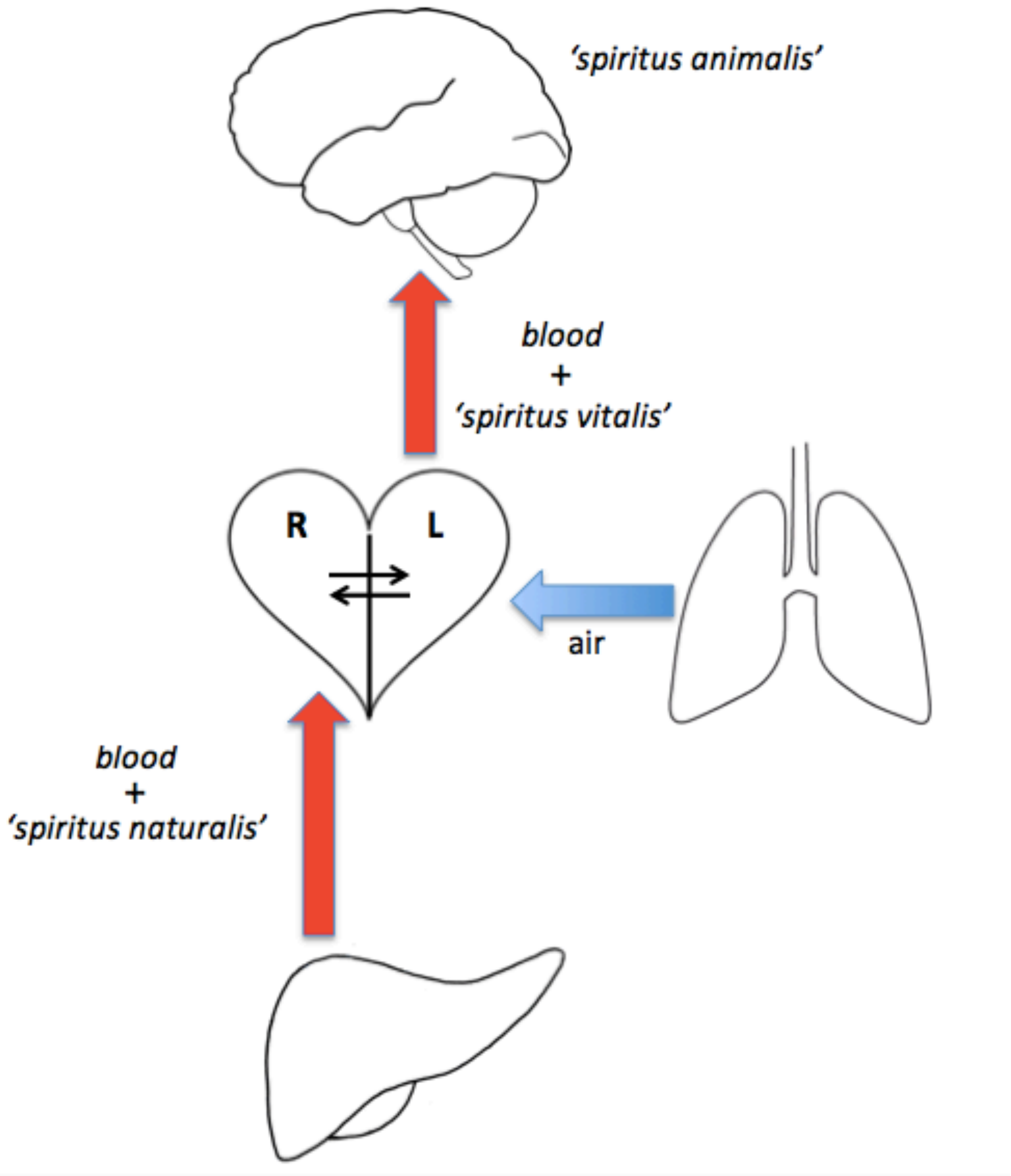

Figure 2. The synthesis of spirits, in three different phases. Schematic illustration of the Galenic model, according to Jean Fernel. The liver converts nutritional substances into blood and also produces a primitive form of spirit ('spiritus naturalis'). In the heart the mixture with air and the power of the innate heat convert 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.

Theory and reality

In general, not only the Platonic but also the Aristotelian representation of nature is highly intellectualistic and theoretical, without obvious links to reality,[77] apart from the fact that the proposed entities are not directly in conflict with daily impressions.[78] Galen, who performed extensive dissections and experiments in animals,[79] cleverly introduced many

[77] For the sake of simplicity, I assume there is a reality.
[78] Cohen (2010), *How Modern Science came into the World*, 16-17.
[79] Mattern (2013), *The Prince of Medicine*, 145-155.

empirical details in his writings, but a substantial part of his theories remains speculative and heavily influenced by Aristotelian teleology: the factuality of a physiological action was often thought to be explained by its purpose. Some of these speculations were rather felicitous, such as the two kinds of spirit (*pneuma* in Greek) he explicitly postulated, though without a shred of evidence. It is not a far cry from vital spirit to oxygen ('aerial', carrying energy) and from animated spirits ('aethereal', signalling) to action potentials of nerve cells. But with regard to other aspects some people dared to criticize Galen as early as in the 16th century. Two of these issues appear in Jean Fernel's Galenic account of the spirits.

A prominent critic was the anatomist ***Andreas Vesalius*** (1514-1564; see box);[80] he discussed these two issues in his – now famous – *Fabrica* of 1543. The first one was the question whether or not there were small channels in the wall (*septum*) between the two chambers of the heart, through which blood from the right half could enter the left one, to be mixed with air. Galen had supposed these channels existed because the wall of muscle tissue between the left and right chamber is very rugged, with elevations, depressions and furrows. Furthermore, they *had to exist* – otherwise the air in the right ventricle could never be mixed with the blood in the left one. Vesalius tried in vain to put a probe through these presumed channels and wondered how the Creator could have made them so tiny that they escaped the eye;[81] in the second edition of his *Fabrica*, twelve years later, he would plainly deny their existence.

The second issue was the 'wonderful web' (*rete mirabile*) of vessels at the base of the brain; an earlier anatomist, Berengario da Carpi (c. 1460-c. 1530) in Bologna, had already expressed his doubts.[82] In an earlier publication Vesalius had still professed his belief in the network and even included it in a composite drawing,[83] but in the *Fabrica* he made it abundantly clear that such a structure might exist in cattle, but certainly not in man.[84] To be quite frank about his error he included a small drawing indicating how he had previously imagined the network (figure 3).[85] Apparently Fernel, physician rather than anatomist, had perhaps not yet noticed this issue in Vesalius' atlas, or he had not changed his views.

Andreas Vesalius (1514–1564)

Vesalius, teacher of surgery and anatomy in Padua between 1537 and 1542 and author of his epochal atlas *De Humani Corporis Fabrica* of 1543, has been so much canonized in later centuries 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 Rhine and the 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 pharmacist at the court of Emperor Charles V. Andreas went to a Latin school in Brussels, after which he took elementary university courses at Louvain; he then 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 but after brilliant examinations he was soon appointed professor of anatomy and surgery.

After completion of the *Fabrica,* Vesalius became personal physician to Charles V; when the Emperor abdicated in 1556, he established a private practice and tried to respond to the careful and restrained commentary on his work written by the then incumbent professor of anatomy and surgery in Padua, Gabriele Falloppio (c. 1523-1562).[1] In 1564 he made a pilgrimage to Jerusalem; on the return journey he became ill on board and died on the isle of Zakynthos, on the Western coast of Greece.

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80 O'Malley (1965), *Andreas Vesalius*.
81 Vesalius (1543), *Fabrica*, 589.
82 da Carpi (1530), *Isagogae Breves*, O5r-O6r.
83 Vesalius (1638), *Tabulae Anatomicae Sex*, plate III.
84 Vesalius (1543), *Fabrica*, 310.
85 *ibidem,* 621.

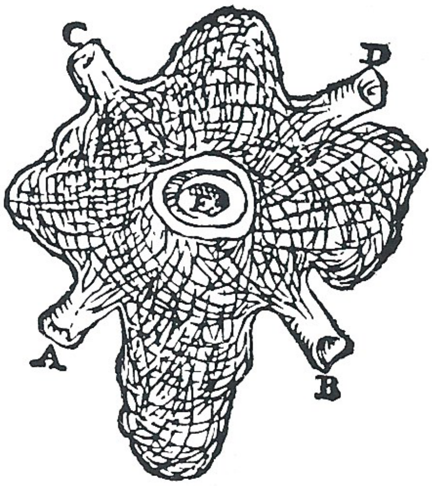

***Figure 3.** Vesalius writes in the legend: "In this figure I made up the network as it must be in order to agree with the descriptions of Galen in his book* On the usefulness of the Parts. *A and B might indicate the arteries entering the skull, soon to disperse in that miraculous tangle; as C and D [I drew] the branches in which the offshoots of this network are joined; they precisely correspond to the other ones in the size of the arteries. E represents the gland receiving the phlegm from the brain."*

The structure of the brain

Having overseen the publication of the *Fabrica* in Basle, Vesalius relinquished his appointment in Padua to seek employment as personal physician to emperor Charles V.[86] His atlas proved controversial for some years, especially because he so often disagreed with Galen,[87] even though the emphasis of his work was on anatomy and not on functional aspects. This restriction was in keeping with his official task at the University of Padua to teach anatomy and surgery. As I indicated above, the medical faculty of Padua, like several other universities, was steeped in Aristotelianism: functional and causal relationships predominated over morphological characteristics, 'why-questions' over 'how-questions'. The most vicious attacks on Vesalius came from Jacques Dubois or Jacobus Sylvius (1478-1555), an influential teacher of anatomy and surgery in Paris, who in his publications declared him 'a madman' (*vaesanus*).[88]

Nevertheless, most of Vesalius' colleagues soon came to recognise him as a master of anatomy, despite some inevitable shortcomings that needed correction in the course of time. While the texts and the exquisite woodcuts, produced by his talented illustrator or illustrators, artistically as well as truthfully described and depicted quite a few anatomical details of brain structures, these niceties were only vaguely relevant with regard to contemporaneous ideas about the function of the brain and about its diseases. The reason is that the action of the brain was generally regarded as a diffuse process, in which all its parts were equally active (the principle of equipotentiality), despite the complexity of its structure. Specialisation of function was thought to exist only in nerves, depending on the sense organs or muscles to which they were connected.

As is clear from the above section about the spirits, a key role in the explanations was assigned to the cavities or ventricles of the brain (figure 4, next page). According to a common – Galenic – assumption, they are involved in two different activities. The first is the production and storage of animated spirits, although precise descriptions of how this occurs have rarely been made explicit. Secondly they are also the medium through which excrements of the brain are evacuated, after extraction of necessary nutrients from blood.

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86 O'Malley (1965), *Andreas Vesalius*, 189.

87 *ibidem,* 218-223.

88 *ibidem,* 238-240 and 246-251.

Figure 4 (from Vesalius' 'Fabrica' of 1543, page 608). *Aspect of the brain from above, after about one third of its height has been removed. The part of the brain that has been cut off from the left side is shown on the right, turned upside down so that the two surfaces fit together. The two symmetrical cavities are the ventricles of the brain. The network covering part of the rounded structures at the floor of the ventricle on either side is the choroid plexus, which according to Fernel – and to many others – has a role in the production of animated spirits from blood. The most anterior (or frontal) part of the cavity continues downwards a bit further than can be seen here, whereas the posterior part curves first downwards and then forwards again. The structure between the ventricles marked 'I' is the corpus callosum ('solid body'); above the level of the ventricles it continues and broadens as a strip connecting the two halves of the brain.*

According to Vesalius, the excretory pathway from the ventricles ends in a funnel-like structure, of which he himself produced a sketch (figure 5, next page). This basin, as Vesalius called it, was located in the midline and formed the lowest part of the cavity above it, called the third ventricle; this ventricle is situated in the middle, between the two lateral ventricles, with which it connects on both sides. Some of the woodcuts in the *Fabrica* indicate the third ventricle from above, but its true shape is not made clear; techniques for preserving and hardening the slack brain tissue would be developed only later. So, the site to where the watery fluid from the ventricles was thought to pass down via the funnel was the gland Vesalius called *glandula pituitaria*, or viscous gland (figure 6, next page). This gland, today known as the pituitary gland or hypophysis, lies burrowed in a separate cavity in the centre of the skull base; normally a thin layer of bone separates it from the extracranial structures. Vesalius, while castigating Galen for believing that the viscous fluid from the brain could pass through the tiny holes in the skull base found more anteriorly,[89] devised a number of channels leading away from the pituitary gland (figures 5 and 6), but provided no information about the manner in which these could pass out of the skull.

[89] Vesalius (1543), *Fabrica*, 32.

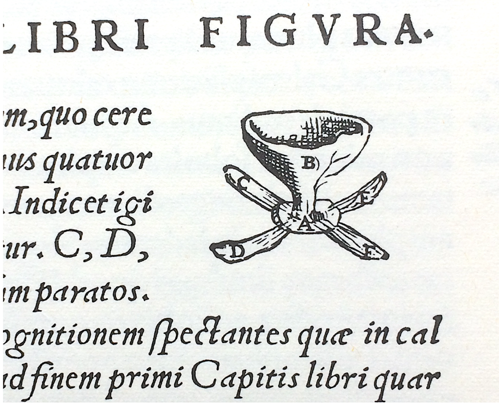
LIBRI FIGVRA.
m, quo cere
ius quatuor
Indicet igi
ur. C, D,
im paratos.
ognitionem spectantes quæ in cal
ad finem primi Capitis libri quar

Figure 5, from Vesalius' 'Fabrica', page 621). *Vesalius inserted this small drawing between the text. The 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 the 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.*

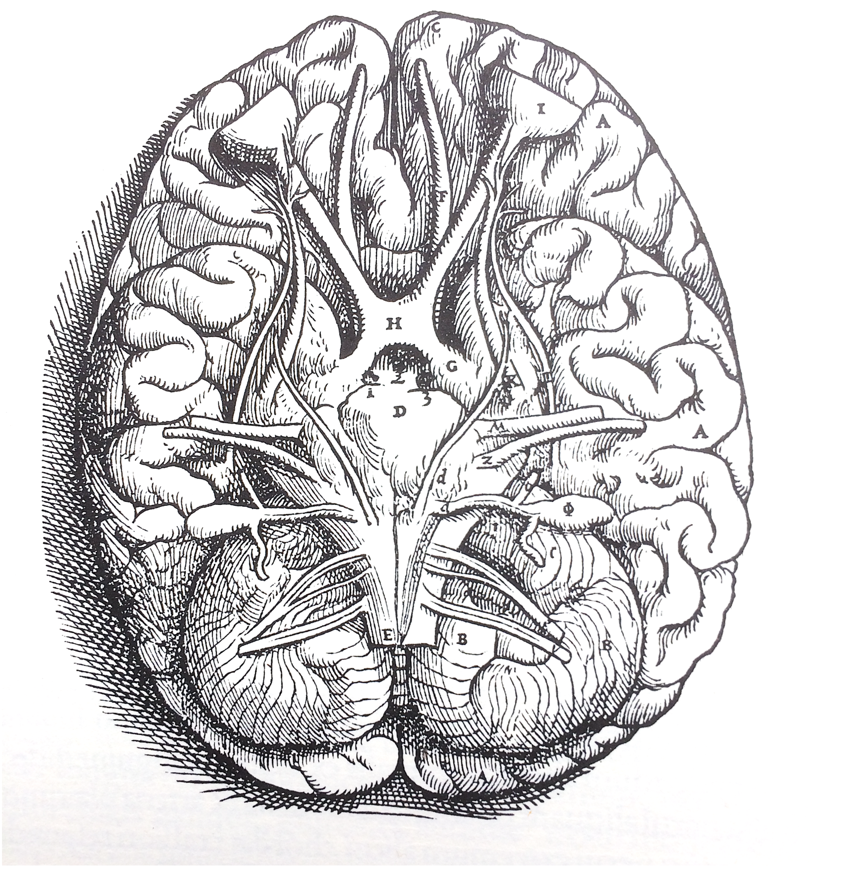

Figure 6, from Vesalius' 'Fabrica' of 1543, page 318). *The brain is seen from below; this point of view is very rarely used until later in the 16th century; in this woodcut the blood vessels are missing and most structures are illustrated rather crudely. The two symmetrical globes at the bottom are at the back of the head and form the cerebellum. In the middle the crossed structure (H) represents the optic nerves, while other nerves arise in pairs from the brain stem (marked 'D'). The pit between 'H' and 'D' is where the funnel-like structure seen in figure 5 is thought to excrete superfluous fluid from the brain into the small gland at the bottom of the brain.*

Apoplexy

In my preface I intimated that the diagnosis of apoplexy is not self-evident, as a circumscribed and uniform natural entity such as a thunderbolt, after which apoplexy was also named (*morbus attonitus*, being stunned). Instead, it is a more or less coherent collection of phenomena defined by physicians – as is the case with almost any disease. The cardinal feature of apoplexy, implied by the Hippocratic aphorism I cited on page 3, is that it strikes suddenly, like a stroke of lightning, and that the patient is immediately incapacitated and may eventually die. But ancient physicians were soon aware that some other diseases also occur in the flash of a moment, for example epilepsy. Therefore additional criteria were needed, through careful observation and recording, in order to allow a distinction between apoplexy and other acute conditions. So, when the frightening and confusing event of someone suddenly falling down occurred again and again in different patients, events separated by weeks or months, the accompanying phenomena were gradually remembered, recorded and subsequently recognized by physicians; eventually they were found to form a recurring cluster of phenomena through which the disease could be identified and diagnosed. In this way it received its status: it was 'framed' by means of its manifestations (symptoms).

The framing of apoplexy

So, the emergence of a specific set of diagnostic phenomena is not an instantaneous and systematic but an evolutionary process: the proper criteria have to mature in medical practice. They are adapted until the profession adopts a more or less workable set of criteria. I will provide a few snapshots of this development instead of a complete review. A first attempt is found elsewhere in the Hippocratic writings (probably 5th century BCE):

> Suddenly a pain seizes the head, while the patient immediately loses his speech and his movement.[90]

Celsus, a Roman from the 1st century CE, had a different emphasis:

> Inactivity of the nerves is a frequent disease everywhere. It attacks at times the whole body, at times part of it.[91]

Galen (130-210), still regarded as the most authoritative ancient writer by physicians in the 16th and 17th century, was a prolific writer: the complete Greek edition of his works, with a Latin translation, counts 22 volumes;[92] some seventeen titles were irretrievably lost with Galen's other possessions when a fire ravaged Rome in 192 BCE.[93] In the vast corpus that is still extant Galen integrated not only the Hippocratic writings (c. 500 – c. 150 BC), but also he critically commented on the work of the Alexandrians Erasistratus (c. 325 – c. 285) and Herophilus (c. 304 - c. 250), methodists like Soranus (c. 100) and dogmatists like Aretaeus of Cappadocia (c. 200).[94] In his books Galen did not separately and coherently deal with each disease in turn. Apoplexy is no exception; therefore the reader has to try and reconstruct Galenic notions from different and sometimes contradictory passages, like pieces of a puzzle. Some key features of the disease are found in a single sentence:

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90 Littré, ed. (1839-1861), *Oeuvres Complètes d'Hippocrate (Diseases II),* vol. VII, 14-15.
91 Spencer, ed. (1935), *Celsus' 'On Medicine',* vol. I, 345.
92 Kühn, ed. (1821-1833), *Claudii Galeni Opera Omnia.*
93 Mattern (2013), *The Prince of Medicine*, 257-267.
94 Karenberg (1994), 'Galen on apoplexy', 85.

> When all nerves have simultaneously lost sensation and motion, the affection is called apoplexy.[95]

The precipitous course is mentioned elsewhere:

> Apoplexy is marked by its sudden onset.[96]

Galen noted that respiration was preserved in these patients – a matter of course at the time, or the patient would be dead – but, he insisted, respiration was abnormally difficult:

> But when the respiration is like-wise affected to such an extent that the patient breathes as in deep sleep, then we speak of apoplexy.[97]

He had also found that the pulse of the arteries in the wrist and elsewhere continued to beat in patients with apoplexy, even without alterations:

> 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.[98]

A first question is therefore how physicians in the 16th century pieced the fragments of the puzzle together to arrive at a set of criteria for the diagnosis of 'apoplexy'. It is useful to begin by consulting a book, published in 1549, devoted to diseases of the nervous system; in fact it was the first of its kind.[99] The author was Iason Pratensis; the surname is a Latinised version of 'van der Velde'; he had studied in Louvain and was a medical practitioner in Zierikzee, also in the southern Netherlands. In the more than twenty pages he devotes to apoplexy, one finds references to Galen (7 times), Hippocrates (6 times) and to six other Greek, Roman or Arab authors (each once or twice); contemporaries are notably absent. About the clinical features he writes:

> 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 keep their pulsations, though these are much more subtle ...[100]

In conclusion, the clinical definition of 'apoplexy' in the 16th century – and also in the 17th century, as will become clear – goes back to ancient Greek medicine and is based on the following observable phenomena:

- a sudden fall on the floor, followed by:
- absence of spontaneous movements;
- absence of sensations;
- persistence of respiration and the pulse.

It is this cluster of phenomena that remains the core criterion for the diagnosis of apoplexy throughout the period of this study; it would not change until the end of the 18th century.

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95 Kühn, ed. (1821-1833), *Claudii Galeni Opera Omnia (De Locis Affectis),* vol. VIII, 208.
96 *ibidem (De Locis Affectis),* vol. VIII, 200.
97 *ibidem (De Locis Affectis),* vol. VIII, 231.
98 *ibidem (De Causis Pulsuum),* vol. IX, 193. Incidentally, it is worth noting how many properties Galen attributed to the pulse; he devoted three other books to the subject (Harris (1973), *The Heart*, 397-431).
99 Pestronk (1988), 'First neurology book'.
100 Pratensis (1549), *De Cerebri Morbis*, 121.

An autobiographical case history

In the period between 1550 and 1700, physicians who recorded actual case histories of patients with apoplexy often only implicitly used these diagnostic criteria: they applied them to make the diagnosis, but did not specify them in their report. Therefore in many cases, at least until around 1650, the reader can only guess what had happened before the doctor came on the scene and which observations had led to the diagnosis. The emphasis of the reports was almost invariably on other aspects, such as the cause of the disease, the treatment given, or the course of the illness.

It is therefore appropriate to present one of the exceptions, a full case history. It is the more exceptional because the patient and the writer are the same person. I first found the story in the chapter on 'Apoplexy' of a book with a collection of medical case histories from various sources that appeared in 1609.[101] It was taken from a book with a collection of prodigious events from pre-biblical times to the middle of the 16th century, published in 1557. The editor of this 'Chronicle' was Conrad Wolffhart (1518 – 1561; figure 7, next page), also known under his humanist name of Lycosthenes. He was born in Rouffach (Alsace) and studied philosophy in Heidelberg. In 1542 he went to Basle, at first as a teacher; three years later he was appointed deacon of the church of St. Leonards.[102] He included his own episode of apoplexy – and his recovery – as one of the 'prodigious events' in the chronicle.

> 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,[103] a horrible incapacity overwhelmed me. I suddenly collapsed on the floor and within 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). 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 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 no rubbing, compresses or other measures could finally warm them. At that time, owing to the humours that were disappearing from the head through 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 completely vanished. [...] Witnesses of my disaster were my very good friends. 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 some products of my pen have some merit for the muses and the critics in the part of my life that is left, I would like to thank God Almighty in the first place, and thereafter Dr. Gratorolo)[...]."[104]

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[101] Schenck von Grafenberg (1609), *Observationum*, 91. This collection was initially published in separate parts; the volume on diseases of the head was first published in 1584, but did not yet contain this story.

[102] Beyer (2012), 'Lycosthenes', Kirchenlexicon.

[103] The 'Aphorisms' (official title 'Apophthegmata') of Lycosthenes would become an important element in teaching at secondary schools, as did Erasmus 'Apophthegmata' (Frank-van Westrienen (2007), *Het schoolschrift van Pieter*, 112-115).

[104] Lycosthenes (1557), *Chronicon*, 640-641.

***Figure 7**. Conrad Lycosthenes (1518-1561). Woodcut, Rijksprentenkabinet, Leiden*

Several aspects of this story are remarkable. First of all, it is exceptional that Wolffhart or Lycosthenes survived this severe illness. In most similar cases, patients would have died within weeks, if not from worsening of the primary cause of the disease, then at least from one of many possible complications of being bedridden, such as bed sores or fevers secondary to infections of the chest and the bladder. In addition, Lycosthenes was a man of letters, while the difficulties he describes of regaining his powers of verbal expression were successful to such an extent that he could again find the words to describe his illness and publish it three years after the event.

What is not exceptional but a rather common experience, even today, is that patients often include common medical notions or causal inferences among their subjective experiences, as happens in the account of Lycosthenes, who intersperses a few comments on 'cold humours' and 'occluded nerves'.

Ambiguities

What the case history also illustrates is that the simple criteria for the diagnosis of apoplexy are not watertight, especially the absence of all senses and of all movements. To begin with the senses, medical treatises in the early modern period often distinguish external and internal senses; the former consist, as now, of sight, hearing, touch, smell and taste, the latter of intellectual activities such as reason, imagination and memory. So 'loss of one's senses' is practically synonymous with the modern term 'unconsciousness'. The reader may recall that Lycosthenes could later write about his fall, its circumstances and other details, so at the time of the event he must have been able to think and to remember – or others must have told him later what had happened. At any rate, the reason that his later compiler and perhaps also his physician nevertheless classified the disease as a case of apoplexy must have been the fact that he was unable to speak. Therefore he could not make clear that he had thoughts and feelings. Bystanders – and physicians – depend on verbal communication to be sure that a person can think and feel; when someone becomes suddenly mute it is not unreasonable to conclude that mental activity had been completely lost. The discovery that language is only one aspect of intellectual functioning came only much, much later.

The problem with 'loss of all movements' is similar: unless patients actually move a limb or other body part, one cannot be sure that they can move at all. To return once more to Lycosthenes, he writes that he was immediately aware that he had lost not only his voice, but also all sensation and movement on the right side. So he must have been able to move his arm and leg on the left side, at least in theory. But again, he was unable to say this; if he had been able to speak and to explain this, his disease might have been classified as 'paralysis' instead of 'apoplexy'. Apparently he showed no spontaneous movements on the left; perhaps he was lying on this 'good' side, or he was too frightened by what had happened to move a single limb. Of course someone might have poked or pinched him, in order to evoke some sort of response. But if this was tried on the affected side and there was no response, why would anyone try the other side? There was no theory to support such an action. 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 wrote that one might even take recourse to white-hot iron,[105] but I suspect he included the sentence for the sake of didactic drama and never tried this cruel procedure himself.

In conclusion, it was left to the discretion of the physician to decide what observations or tests were necessary to decide whether all sensations and movements were absent and whether the results satisfied the criteria for arriving at a diagnosis of 'apoplexy'. Since this information has been rarely recorded, at least in the first hundred years of the study period, I will have to abide by the diagnoses that were made and I will have to accept some inherent incongruity between physicians.

Notions about apoplexy in the general population

My study is concerned with the written legacy of academic medicine; therefore I cannot claim to present a picture of what information patients with apoplexy or their relatives would have or receive about the illness. However, some impressions can be gleaned from the work of Michael Stolberg, who went through hundreds of letters from the 16th and 17th century in which patients wrote to relatives or friends with accounts of disease. The dangers of a stroke, he reports, appear to have been widely known among the general population, including the more technical term 'apoplexy'. Warning signs of such an event were extreme redness of the face or swollen veins (the physicians' 'plethora'), dizziness, a state of confusion, coldness in the head, a feeling of heat in the body, or heart palpitations. Ideas about causes revolved around a sluggish flow of unhealthy, corrupted blood or pressure on the brain from its cavities.[106] On the whole, these ideas broadly reflected medical opinions, as I will show; of course we lack information about the illiterate part of society.

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[105] Pratensis (1549), *De cerebri morbis*, 422.

[106] Stolberg (2011), *Illness*, 92-94.

Chapter 4

CAUSES OF APOPLEXY, 1500-1625

Locating apoplexy: in the cavities or in the tissue of the brain?

The brain as an object: the role of the ventricles challenged

Occluded ventricles, yet sensation and motion

The importance of brain tissue becomes textbook material

Also causes outside the brain, through obstruction of blood vessels?

The fluids thought to cause obstruction and apoplexy

Contributory factors

Additions to the diagnostic 'frame' of apoplexy

Treatment

Back to causes of apoplexy: the movement of blood

This chapter is dedicated to the actual development of ideas about the causes of apoplexy in the second half of the 16th and the first quarter of the 17th century. According to the Greek version of brain function all aspects of sensation, movement as well as the intermediate processes of imagination, ratiocination and memory depended on the synthesis of 'animated spirit' from its somewhat less aethereal precursor, 'vital spirit'. This process was thought to take place in the cavities of the brain, the ventricles; from there the spirits were supposed to flow into the nerves of the appropriate body parts. The notion that the content of these cavities was more essential than the surrounding brain tissue was not surprising: after all, the point of drinking is the fluid rather than the cup, while 'fluidism' was an important principle in ancient medicine. As recently as at the end of the 18th century the notion that the ventricles were the 'organ of the soul' once again captivated a serious anatomist.[107] The shape of the lateral ventricles further enhances their functional importance: they seem almost carved out in each half (right or left) of the brain,[108] while at the floor of each of the cavities gland-like structures were found, rich in blood vessels from which the spirits could be thought to emanate (figure 4, page 29). All this fitted the Aristotelian principle of 'purpose', a pervasive element of Greek natural philosophy.

The clinical features of apoplexy, with its sudden cessation of all brain functions while breathing and arterial pulsations continues, suggest a sudden interruption in the traffic of spirits between its arrival in the brain and its flow into the nerves. So it is not surprising that initial explanations of apoplexy revolved around obstruction within the ventricular system. However, in the course of time between 1550 and 1625 ideas about the function of the cavities of the brain would change. Of course these changes would have important implications for the explanation of apoplexy. Therefore my story will sometimes switch from disease to function.

Apart from the issue of location, a further question is the nature of the material thought to cause the obstruction – often one of the four classical humours, sometimes other substances. The six principal authors I selected by means of citation analysis (page 10) will all make their appearance, as well as others if appropriate. The ordering of the narrative will be topical rather than by author. Within these topics I have given precedence to logical rather than chronological order; also reliance on publication date as an ordering principle is somewhat hazardous, because lecture notes of famous teachers were sometimes published late in their lifetime or posthumously, while the influence of their ideas may well have preceded the printing press.

Locating apoplexy: in the cavities or in the tissue of the brain?

Blocked ventricles

The Galenic version of the causal factors in apoplexy can be found in several different textbooks, for example in the first monograph on diseases of the nervous system, published in 1549, a book I mentioned earlier in relation to the clinical features of apoplexy. Its author was ***Iason Pratensis*** (educated in Louvain, practising in Zierikzee):

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[107] Sömmerring (1796), *Das Organ der Seele*. The philosopher Immanuel Kant, invited to add a postscript, preferred to stay on the fence about the location of the soul.

[108] Varolio, in proper Aristotelian tradition, opposed the term 'ventricle' for the two smaller cavities in the midline; in his view these spaces were just left over between the two halves of the brain, without 'purpose' (Varolio (1573), *De Nervis Opticis*, 11r).

> All apoplexies arise because the mental power cannot flow down to the lower parts of the head, owing to a certain disposition similar to inflammation taking place in the brain, always accompanied by fever and eminently fatal, more than other [causes]. Or [the cause is] too cold phlegm, thick and slow juices abundantly and completely filling the main ventricles of the brain and badly damaging its very body.[109]

The main point here is "thick and slow juices abundantly and completely filling the main ventricles of the brain". Whether it is always phlegm is a matter I will discuss later. Incidentally, fever and inflammation are subjects that other physicians almost never mention in relation to apoplexy, except as a later complication. Probably Pratensis had met in his practice one or more fatal cases in which an 'apoplectic state' (i.e. 'a patient does not move or react but still breathes') was accompanied by high fever, while he was led to believe that the onset had been sudden. His description highlights the unavoidable complication that the notion of apoplexy I defined earlier on was roughly but not completely identical in every physician's mind.

Jean Fernel (Paris) explained the cause of apoplexy as follows, in his didactic style:

> The cause of this 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 ....

Again the key point is "abundant filling of the ventricles". But then Fernel mentions an alternative location, at odds with conventional, Galenic explanation of apoplexy:

Or elsewhere?

For he continues the sentence about cold phlegm overstuffing the ventricles as follows:

> .... or when it ever so slightly obstructs or narrows the arteries of a wonderful network, through which the spirits flow from the heart into the cavities of the brain. Then indeed the cavities, defrauded of inflowing spirits, can thereafter supply nothing to the nerves for sensations and movements, and soon the creature necessarily collapses.[110]

This new possible location Fernel mentions is the site of the arteries forming the 'wondrous network' at the base of the brain. But, as I explained before (page 27-28), these arteries are a fictitious entity, at least in man. The reason Fernel referred to this location is that he had performed a post mortem dissection (autopsy) on a patient who had died from apoplexy. He reported this in a book published six years before his 'Medicina', with the intriguing title 'About hidden causes of things.' Fernel had found a lesion below the brain, at its base:

> Once I saw that a man, [previously] in perfect health, had suddenly collapsed by 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. Therefore I thought 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 only the 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.[111]

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[109] Pratensis (1549), *De cerebri morbis*, 423.
[110] Fernelius (1554), *Medicina* (Pathologia), 133.
[111] Fernelius (1548), *De Abditis Causis*, 267.

The first published post mortem dissection of the brain after apoplexy: a furtive glance
We must pause a while here. The sentence "I thought the cause of death was worth investigating" sounds rather harmless at first sight; yet it implies a momentous decision, that is, to open the skull of the tragically deceased man. Such a procedure does not only require much effort, expertise and equipment, it also implies violating the integrity of the human body, shaped – as many believed – after a divine example. I mentioned this taboo before (page 18-19). Thus, Fernel must have had doubts about the usual, Galenic explanation that the cavities of the brain were stuffed with phlegm. That such an event in the brain could be the result of a punch on the eye is indeed improbable, he may well have thought.

That I decided to omit, in general, reports of 'apoplectic states' caused by external trauma such as blows and falls is not relevant in this case, because it was the very sequence of events – a blow and an 'apoplectic state' – that prompted Fernel to get to the bottom of the causes of this condition and to produce the first report of a dissection of the human brain after presumed apoplexy.

That Fernel's dissection is breaking new ground can help the reader to understand why his report is not very precise. First of all, the blood vessels of the eye are enclosed in the orbit, a bony cavity largely separated from the encasement of the brain; it is not impossible to open it, but it is certainly not visible at first sight after the top of the skull has been taken off, according to the usual procedure. More important is the possible contradiction between the comment that the membranes of the brain were intact and the finding that there were two spoonfuls of blood at the base of the brain. Was the blood found inside or outside the hard membrane (*dura mater*) that surrounds the brain? The fact that Fernel concluded the extravasated blood must have compressed the 'net-like structure of arteries' suggests that it was below the membrane, that is, on its outside, where Galen had situated the network – a structure that does not exist in man, as explained on pages 27-28. On the other hand, a pool of blood between the bony skull base and the hard membrane is unknown in modern pathology, except perhaps by extremely violent trauma. Also, and importantly, Fernel concluded these arteries must have been compressed by the pool of blood, even though he cannot have seen them – at least not in the form of the network Galen had described; he just assumed they were there. On the same page Fernel briefly mentioned that he had dissected another patient after 'apoplexy' (no details); he found that a thick, viscous fluid compressed this same arterial network that he cannot have actually seen. So he continued:

> Apoplexy can occur when these arteries are blocked or compressed, because then the brain does not receive any spirit from the heart via the arteries in question; necessarily the movements and sensations dependent on it are lost. Someone who noticed this [before] rightly said, in my opinion, that apoplexy occurs when the common pathways between the brain and the heart are interrupted.[112]

So, to sum up Fernel's contribution with regard to the location of apoplexy, he suggests that, broadly speaking, also obstructive events such as collections of blood or phlegm at the base of the brain might prevent the transport of vital spirits from blood vessels to the brain. This conclusion rests on rather incomplete observations, in fact not more than a cursory peek. The problem that he reported compression of tangled blood vessels that he cannot have actually seen does not in itself invalidate the possibility that rapid extravasation of blood or other at the base of the brain can cause apoplexy. At any rate, his observation of the man who died after been hit on the eye was cited many times by later generations of physicians.

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[112] *ibidem,* 267-268.

Dearth of clinical and pathological details

Fernel did not provide clinical information about his second patient, in whom he thought phlegm at the base of the brain had obstructed the access of vital spirits to he brain. Indeed one wonders whether this pathological state can have occurred instantaneously. The same applies to two more reports of dissection published in the 16th century. The first is by ***Louis Duret*** (1527-1585), from 1568 onwards professor of medicine at the *Collège de France* in Paris.[113] In his commentaries on Hippocrates' *Coan Ideas*, which appeared posthumously, he briefly alludes to dissections he performed in two dignitaries who had died after apoplexy:

> Apoplexy arises either because animated spirit is prevented from leaving the brain, or vital spirit from entering it. 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.[114]

So, Duret explicitly adds a second main category of causes of apoplexy to Fernel's impeded entrance of vital spirits, one that had been implicitly suggested from the time of Galen: impeded exit of animated spirits. The site of obstruction was the ventricular system of the brain, perfectly in line with Galenic doctrine. But again, the observation is cursory: there is no information about a possible source of the haemorrhage. And again clinical information, about the symptoms of the two patients, is also lacking.

I encountered a similar paucity of details in a report by Duret's contemporary Marcellus Donatus (1538-1602),[115] personal physician of the Duke of Mantua; he dissected another dignitary:

> I was charged with dissecting the administrator of her Highness Maria Justiniana de Arrivabene [in Mantua], who had died from a severe Apoplexy. I brought with me as witnesses the gentlemen Hippolitus Genifortus from Mantua and Ludovicus Cangerla from Vicenza, both practicing 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 had been opened,[116] 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.[117]

To begin with, a noteworthy novelty in this case is the presence of colleagues as witnesses. Nevertheless, one is led to suspect that actually the three physicians did not find very much. For the presence of 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, as was well known at the time. The suggestion is, however, that the quantity of fluid was excessive, as was the quantity of blood in the vessels of the brain. But such a judgement presupposes extensive practice in dissecting brains, a level of experience that seems quite unlikely. And, once more, there is no information about the phenomena that led to the diagnosis of apoplexy.

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113 Hirsch (1884-1888), *Biographisches Lexikon*, volume II, 244.

114 Duretus (1588), *Hippocratis Coacas Praenotiones*, 366.

115 Hirsch (1884-1888), *Biographisches Lexikon*, volume II, 202.

116 The temporal arteries (according to modern nomenclature) are situated between the skin and the skull; since the skin and skull had been removed at an earlier stage of the dissection, the author is probably referring to large arteries in the brain itself.

117 Donatus (1586), *De Medica Historia Mirabili*, 59v.

The brain as an object: the role of the ventricles challenged

I return to Fernel's dual explanation of apoplexy, since he attributes it to overfilling of the ventricles as well as to collections of fluid at the base of the brain. With regard to the former cause, there is an inkling of doubt in his expression 'despite forming the brain's excrement' (*licet proprium cerebri excrementum sit*). For how is it possible that the fluid in the cavities of the brain is not only the medium where the 'animated spirits' are produced or at least stored, but that at the same time it functions as a reservoir for the waste of the brain, like urine from the kidneys, bile from the liver and saliva from glands in the oral cavity? This excretory function had also been described and even illustrated in a partly fictitious drawing by Vesalius (figure 5, page 30), but Vesalius was an anatomist, not only by appointment but also by nature; he had no qualms about pathways of spirits that could not be seen anyway. But to assume a single structure with a double function was anathema to most minds that had been imbued with Aristotelian teleology. Inevitably, some people did worry.

The brain in the physician's hands

Costanzo Varolio (1543-1575; see box) was a young teacher of anatomy at the University of Bologna.[118] In 1572, shortly before his departure to Rome, where he was soon to die, he wrote a letter to ***Hieronimus Mercurialis*** (Girolamo Mercuriale; 1530-1606) in Padua, the town where Varolio had studied before Mercurialis' appointment to an Ordinary chair of theoretical medicine in 1569.[119] Mercurialis had at first served as court physician and diplomat and enjoyed a great reputation because of his expertise in ancient Greek medical texts.[120] It is clear from the text of Varolio's letter that he regarded Mercurialis, his senior by 13 years, as a kind of mentor, and that he appealed to him as an impartial judge about his new findings about the anatomy of the brain. The letter was published in print a year later, together with Mercurialis' response and Varolio's rejoinder.[121]

Costanzo Varolio (1543-1575)

Little is known about Varolio's youth, except that he was born in Bologna as son of a citizen whose profession is unknown. He studied medicine at the University of Bologna and graduated in 1566. After a period in Padua, the senate of Bologna appointed him in 1569 to the professorship of anatomy and surgery (figure 6); he focused his anatomical investigations on the brain.

Some controversy had arisen between Varolio and his colleagues in Bologna; therefore the young anatomist sought support from Mercurialis. The trouble had started when Varolio had found a new method of studying the anatomy of the brain, especially of the cranial nerves and the ventricles. Through his new technique of dissection he managed to detach the intact brain of a cadaver from its attachments to the skull base, by carefully cutting the nerves and blood vessels traversing the skull base, so that in the end he could lift the entire brain from the skull and turn it upside down; this allowed a full view of the basal structures of the brain (next page). I should explain that in life as well as after death the brain has a slack and flabby structure; it becomes even more liquid as decay sets in. Vesalius had also illustrated the base of the brain (figure 6, page 30), more artistically but with less

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118 Tubbs, et al. (2008), 'Costanzo Varolio'; Zago and Meraviglia (2009), 'Costanzo Varolio'. The drawing is from the Biblioteca Communale di Bologna.

119 Hirsch (1884-1888), *Biographisches Lexikon* volume 4, 209. In 1587 Mercuriale would move to Bologna.

120 Mercurialis (1603), *Praelectiones Patavinae*.

121 Varolio (1573), *De Nervis Opticis*. The letter was republished in 1591, together with an anatomical treatise that had not been published during Varolio's lifetime.

anatomical accuracy than Varolio; probably it was made a later stage of the dissection, after the upper parts of the brain had been cut away from the top down, as shown in figure 4 (page 29).

This was a major step. Removal of the brain from a cadaver had far greater implications than that it merely allowed the anatomist to turn it upside down and study its base in more detail. The new procedure reduces the brain to an object, disengaged from its body and from its abstract connotations – an object that can be isolated, handled and opened.

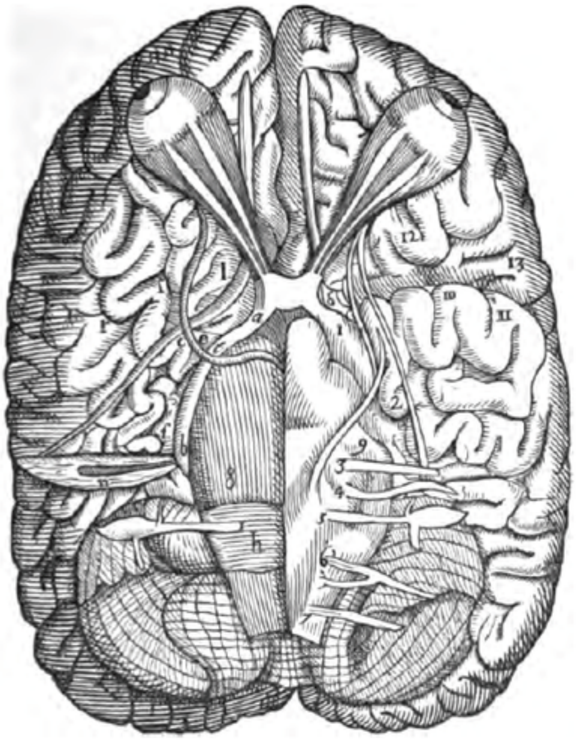


Figure 8. *View of the base of the brain, after the entire brain has been detached from the skull and turned upside down (Varolio 1573). The main point Varolio wanted to make, not actually relevant for the issue of the function of the ventricles, is that the optic nerve (red arrow) continued much farther backwards (to the bottom of the drawing) than had been assumed before. Incidentally, Varolio discovered the 'bridge' (*pons *in Latin, the transversely striped structure marked 'h').*

Ventricles as the sewer of the brain?

Having discussed several matters unrelated to the function of the ventricles, Varolio prepares his addressee for an unconventional proposition by means of a circumlocutory and polite phrase:

> Very famous 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 will 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 would like you to think that I submit it in a doubtful manner rather than as a certainty.[122]

Varolio then describes the gland-like structures at the bottom of the lateral ventricles (currently termed 'choroid plexus'; see figure 4, page 29); then, by analogy with other glands, he submits his conclusion that they must have an excretory function:

[122] *ibidem,* 7v-8r.

Presently it is known to all that phlegm drips from the brain to the palate via the infundibulum;[123] 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.[124] [......] 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 spirit, since (as has been said before) more functions can be assigned to a single part [of the body].[125]

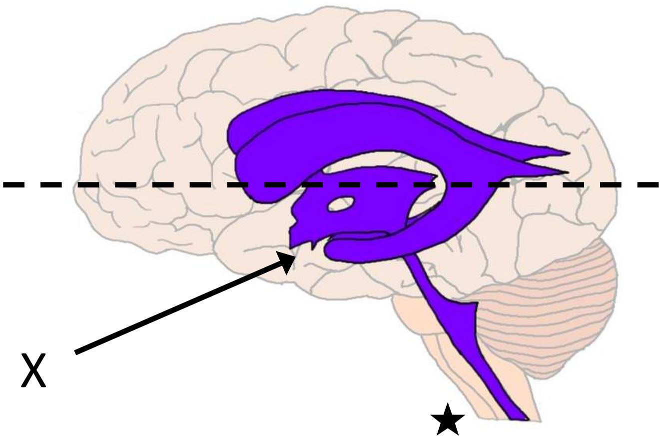
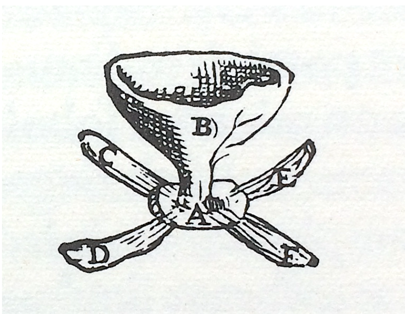


***Figure 9**. Modern schematic drawing, in which the ventricular system of the brain is super-imposed on the brain tissue. In reality the two arched ventricles are situated in each half of the brain (lateral ventricles). The two smaller ventricles are in the midline: the 3rd ventricle lies between the two lateral ventricles, the 4th ventricle between the brain stem (asterisk) and the cerebellum. The dotted line corresponds to the plane of section in Figure 4 (page 29, by Vesalius). The arrow marked with 'X' points at the lowest part of the 3rd ventricle.*



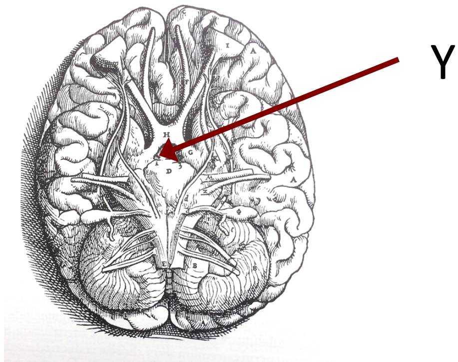


Figure 10.
***Left:** this is once more (figure 5, page 30) the funnel ('B') drawn by Vesalius, which corresponds with the lower part of the 3rd ventricle. The structure Vesalius marked with 'A' is the gland that lies buried in the base of the skull, close to the lower part of the 3rd ventricle, but – other than in Vesalius' speculative drawing – it does not form part of the cavity. The present name of the gland is 'pituitary gland', which recalls the association with phlegm; its other name is 'hypophysis'. The channels C, D, E and F are fictions of Vesalius.*
***Right**: this is a small version of figure 6 (page 30), which represents the base of the brain as represented by Vesalius. The arrow marked 'Y' indicates the site where the hypophysis has been cut off from its stalk; it remains left in the bony skull base. It is important to be aware that the lower part of the 3rd ventricle is very close to the skull base; in figure 9 it seems to be covered by brain tissue, but in fact these two lobes on both sides of the brain reach further down than the structures in the midline. The anatomical arrangement in the midline led Renaissance anatomists to believe that fluid flowed from the ventricles to cavities of the nose and throat, via the various openings in the skull base for nerves and blood vessels.*

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[123] '*infundibulum*': Latin for 'funnel', the lower part of the 3rd ventricle.
[124] Varolio (1573), *De Nervis Opticis*, 9r.
[125] *ibidem,* 9v.

I added figures 9 and 10 on the previous page to illustrate the manner in which Varolio envisaged the excretory pathway of the brain fluid; he must have read the speculations on this pathway by Vesalius, whom he admired. The idea of phlegm dripping from the brain to the base of the skull to the nose and throat may seem unfamiliar to modern readers, but it was entirely in keeping with ancient ideas.

Animated spirits conveyed by the tissue of the brain?

Let me return to the reaction of Mercurialis to Varolio's proposal. He flatly disagreed. After many compliments about the new anatomical findings, he opposed the idea of an excretory function of the ventricles, since this could not but interfere with the production of 'animated spirits':

> Insofar as you displayed that peculiarly sharp mind of yours when you explained the function of the ventricles of the brain, you have (please allow me to say this) to the same degree 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 boiled and perfected, in a furnace 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.[126]

Mercurialis shores his response with several citations from Hippocrates, Plato and Galen. Varolio replied, after profuse expressions of gratitude towards Mercurialis, that he persists in his opinion about the excretory function of the ventricles. He goes as far as proposing a different location for the spirits and writes that he has found some support in Galen's writings for the option that the spirits reside in brain tissue:

> Galen says in *De usu partium* (book 8, chapter 13) that animated spirit is contained in large amounts in the entire body of the brain, and similarly in the body of the cerebellum, to which he assigns [the function] of forming the origin 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 transmits 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,[127] why does it not instead flow in the same way, without cavities and fistulas, from the brain to fewer and much closer parts?[128]

So Varolio was faced by a double 'purpose' of the cerebral ventricles: excretion of waste products as well as transport of 'animated spirits'. His solution was to interpret Galen in such a way that the traffic of spirits is attributed mainly to the substance of the brain and the cerebellum, not to the ventricles. He heavily leaned on the commonly accepted fact that most nerves in the skull originate from the brain stem (marked by an asterisk in figure 9 on the previous page), which does not accord with the small size of the fourth ventricle in comparison with the large lateral ventricles, in an area where very few nerves begin.

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[126] Mercurialis (1573), 'Letter to Varolio', 23r-23v.

[127] The spinal cord, with all its nerves to arms, trunk, and legs, is regarded as a continuation of the cerebellum.

[128] Varolio (1573), *De Nervis Opticis*, 26r-26v.

Normal ventricles in victims of apoplexy?

Varolio also had to counter Mercurialis' objection that assigning the transport of animated spirits to the brain tissue itself would undermine the time-honoured belief that blocked ventricles were the cause of apoplexy and other acute brain disorders. He briefly entertained the possibility that in those cases expanded ventricles might squash the spirits contained in the substance of the brain. But then he immediately rejected that possibility, by linking a passage in Galen 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 from Apoplexy, in whom (please believe me) no greater quantity of excrements is found than one usually finds in all others.[129]

If the pathological changes causing apoplexy do not occur in the ventricles, Varolio reasoned, they must happen elsewhere, i.e. at the base of the brain, at the origin of the spinal medulla (that is, the part within the skull, presently called the brain stem) arises.

His most surprising argument – apart from a helpful citation from Galen to placate Mercurialis – was the empirical claim that post mortem studies of patients who had died from apoplexy showed the same quantity of fluid in the ventricles as other people. Although this early glimpse of post mortem findings may seem important in the light of later developments, the reader has difficulty in deciding what weight one should attach to this observation. On the one hand it was a casual, almost offhand remark, not substantiated with details about person, time or place, let alone with support of witnesses. On the other hand Varolio's exclamation "please believe me" suggests the observation was his own, and not just hearsay.

Why did the striking finding that patients with fatal apoplexy had normal ventricles fail to be publicised? Presumably, I venture to guess, because the finding did not agree with received opinion – these facts were inconvenient, unwelcome, unheard of, things one might gossip about but that should not be openly discussed. The same cognitive distortion that can cause physicians to see things they wish to see even in their absence can cause them to deny or at least suppress things they would rather not see. This is what caused Varolio to write, when he had been met not only with disbelief but also with accusations of cheating when he showed that structures at the base of the brain differed from ancient descriptions:[130]

> 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.[131]

Observation and speculation

It was not only a question of looking that made it difficult for Varolio's incredulous colleagues in Bologna to accept his findings. They were looking at an unfamiliar object: the brain, which Varolio managed to remove as a whole, an unwieldy, soft and sagging mass of some three pounds, subsequently turned upside down. Varolio did not just look intently at what nature presented to him, he pried into its tissues to obtain a better look and to provide accurate descriptions. Varolio tried to emulate Vesalius, who had again and again in vain pushed his probe into the recesses in the wall between both ventricles of the heart in

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[129] *ibidem,* 28r-28v.
[130] *ibidem,* 13v.
[131] *ibidem,* 11r.

attempts to find the channels through which, as Galen claimed, blood and air were mixed – to conclude in the end that there were no such channels.[132] So the empiricism of Vesalius and Varolio was not just a matter of accurate observation versus received wisdom. It was also a matter of asking questions from nature, or, to borrow Cohen's term, *coercive empiricism*.[133]

I am not the only historian of medicine to note that Varolio was the first to propose that animated spirits are contained in the brain substance, instead of in the ventricles.[134] Varolio based this conclusion, with the implication that apoplexy should involve the tissue of the brain rather than its cavities, on two arguments. One was the – almost secret – news that the ventricles could have a normal aspect in patients who had died from apoplexy, the second was the anatomical disproportion between the size of the different parts of the ventricular system and the site of origin of nerves within the skull. This means there was still a fair element of speculation. Nevertheless, Varolio seems to have allayed the doubts he initially professed in his rebuttal to Mercurialis:

> If someone would counter that Plato, Galen and others had located the animated spirits in the cavities of the brain, I would not disgrace myself, I think, if I responded that Plato is a friend and Galen is a friend, but that the nature of things is even more a friend.[135]

This appeal, a well-worn trope,[136] has the novelty that the usual appeal to 'the truth' as the highest authority is now replaced by 'nature'.

Occluded ventricles, yet sensation and motion

Two separate post mortem observations of young children contributed the final pieces of evidence to undermine the notion that the function of the brain depended on its cavities. Both children had died after progressive enlargement of the lateral ventricles. The importance of these reports is that they included not only a description of the abnormalities of the brain in these two children, but also an essential observation from the time that they were still alive: both had been able to move and interact. This unique combination of clinical and pathological observations, a landmark in the history of medicine, was bound to raise questions about the relevance of the ventricles for the transport of 'animated spirits'.

One of the two reports was published at the middle of the 16th century, the other at its end; they did not catch immediate attention, but as time went on they were cited more and more often. It was no other than ***Andreas Vesalius*** (1514-1564) who reported the first instance. It was published in 1555, in the second edition of his famous *Fabrica,* as follows:

> 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 could compare with that mass. This was the affection the ancients called hydrocephalus, from water retained and gradually collected in the head. However, in this girl the water was not found between the skull and the outer membrane that surrounds it, or between the skull and the skin (books of physicians teach us that water is found there on other occasions). But here it was in the cavity of the brain itself,

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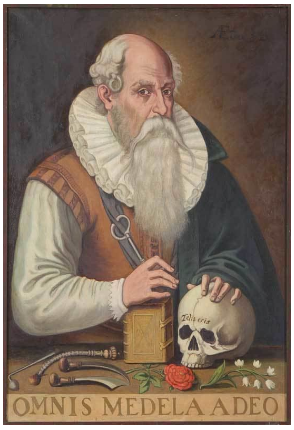
132 Vesalius (1555), *De Humani Corporis Fabrica*, 734.
133 Cohen (2010), *How Modern Science came into the World*, 113-132.
134 Neuburger (1879), *Gehirn- und Rückenmarksphysiologie*, 125.
135 Varolio (1573), *De Nervis Opticis*, 27v.
136 The expression "Amicus Plato, amicus Aristoteles, magis amica veritas" or versions thereof, which dates from antiquity, was quite commonly used in the 17th century (Shapin (1994), *Social History of Truth*, 117n).

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 abnormally expanded. It was almost in the manner in which we see in new-born children the joining of the frontal bone and the bones at the side, where they are generally close to each other; in very young children they appear membranous, over a remarkable distance and width. Otherwise the cerebellum and the entire base of the brain were normal, as were the origins of the nerves; furthermore I found absolutely no water in any site other than in the ventricles of the brain that had so much expanded, as I said. Up to the time of her death the girl had the complete use of all her senses. And as often as her head, when I saw her a few days before her death, was moved by those around her and was lifted ever so little, severe cough immediately troubled the girl, with difficult respiration and an amazing redness of her entire face, congestion of blood and a profusion of tears. With regard to the rest of the body her condition was average. [....] 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.[137]



Guilhelmus Fabricius (1560-1634)

Wilhelm Fabry, the 'father of German surgery', was born in Hilden, Nordrhein-Westphalia, where a bust of him marks 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 had shown talents for acquiring ancient and current languages; thanks to the support of Karl van Utenhove (1536-1600), a Flemish humanist and friend of the family, he could continue his studies. He might have gone to university, had not the Thirty-Years' War caused a complete upheaval of normal life. Eventually Wilhelm had to give up his ambition of being a doctor; he became apprentice to a surgeon, first in Neuss and in 1580 in Düsseldorf. His master there was Cosmas Slotanus, surgeon at the ducal court; he had been taught by Vesalius. Wilhelm was not only introduced to modern anatomy but also he learned a lot from the physicians at the palace. When Slotanus died in 1585, Fabry began a life of wandering. He first practiced in Metz and then Geneva, where he married Marie Colinet, herself a surgeon and obstetrician. Further peregrinations included Cologne, where a young son died, and several Swiss towns; two daughters died in Lausanne from the plague in 1613. He travelled far and wide to patients from wherever he lived, as his fame increased. In 1615 Fabry finally settled in Berne, where he was appointed surgeon to the town and canton. His later years were troubled by gout. On his death in 1634 left a wife and a son Johann, also surgeon; his other seven children did not survive him.

I reproduce a second case report, not only because it once more describes that at least some mental functions were retained in the presence of greatly enlarged lateral ventricles. Also it is likely that the similarity of the two observations, made in different locations and at different times, greatly contributed to their veracity. Multiplicity and consistency are two of the seven criteria Steven Shapin identified for the assessment of scientific testimony by the founders of the Royal Society, in the next century.[138] The impact on the medical community of the two case histories together must have been far greater than twice that of a single report. Indeed the author of the report, ***Guilhelmus Fabricius*** or Wilhelm Fabry (1560-1634; see box) is among the six physicians who were most often cited by the authors of the first two monographs on apoplexy to appear in the 17th

[137] Vesalius (1555), *De Humani Corporis Fabrica*, 24.
[138] Shapin (1994), *Social History of Truth*, 212-232.

century (page 10). Actually, Fabry was not a physician but a surgeon.[139] In 1598 he started to publish case histories, of which he had kept notes. Eventually each installment contained one hundred surgical observations (*centuriae*). The events were mainly from Fabry's own practice, but also contained memorable case histories his colleagues sent him by letter. Despite Fabry's lack of academic schooling his circle of correspondents included many physicians, including Johannes Crato von Krafftheim (1519-1585),[140] his senior by some 40 years, whose observations – medical rather than surgical *centuriae* – were also published in serial form, though posthumously. A collected edition of Fabry's *centuriae*, including unpublished observations, appeared in 1641 in Latin, followed by several other editions and translations.[141] The story of the hydrocephalic child had occurred in 1594; it was as follows:

> In a region of Cologne called *Ehrestrasse* I saw several times a boy, son of parents in robust health, whose head had grown to an incredible size; its circumference was one and a quarter Cologne cubits and the distance between one ear and the other was more than one and a quarter cubit.[142] He had not been born like this, for 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. Hence it happened that the undulations and gyrations of the brain were not [separately] visible but were all swollen.
>
> The hard membrane as well as the tender membrane was intact but they were so much distended that they [tightly] covered the entire brain. The skull was similarly distended, but generally in its cartilaginous rather than in its bony parts. It can still be visited in my Museum. The third ventricle appeared not to be merged with the two anterior ventricles. In the fourth ventricle we found a small amount of some viscous material. At the base of the brain all other things were normal and we did not find an opening through which that serous fluid had been transported to the head, though we accurately inspected everything.[143]
>
> Finally, the heart and lungs, diaphragm, liver, stomach, spleen and kidneys were completely healthy. [....] Indeed he ate, drank, 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. However, he was completely robbed from mental actions and senses that are dependent on the brain, such as thought, speech, vision, hearing, etc. Also he hardly voluntarily moved his arms and legs, lips, eyelids and eyes, but quite often involuntarily; that is to say, they were continuously moved and shaken, but without pain.[144]

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[139] Jones (1960), 'Fabricius Hildanus', 112-134.

[140] Hirsch (1884-1888), *Biographisches Lexikon* volume II, 102.

[141] Jones (1960), 'Fabricius Hildanus', 121.

[142] 'Cubit': the length of the forearm (between 44 and 53 cm, depending on the region). So the head circumference of this boy would have been about 73 cm; for a child of four years in The Netherlands in 2018 the average head circumference is 51 cm.

[143] The description of the two hydrocephalic children is sufficiently accurate to recognise the disease, in retrospect, as obstruction or other narrowing of the tiny channel connecting the third and fourth ventricle; the two cavities and the connecting channel (aqueduct; see figure 9, page 44) are all situated in the midline of the brain. Normally cerebrospinal fluid is produced in the lateral ventricles, by the choroid plexus (see Vesalius' illustration in figure 4, page 29); via the fourth ventricle it is excreted to the space around the brain.

[144] Fabricius (1641), *Centuriae*, 25-26.

Together the two case histories of hydrocephalic children are relevant in the context of apoplexy because later generations would use them as an argument to question the role of the ventricles as the site of production or storage of ‘animated spirits’. The two observations not only reinforce each other; three separate aspects are important.

The key feature is the accompanying story of the symptoms that preceded the fatal outcome. No matter how unusual or amazing the description of post mortem findings in general may be, structural abnormalities are only useful in understanding disease if they can be related to the functional abnormalities that preceded them. True enough, the ‘anatomy of disease’ is a vital element in the building of medical knowledge, but it is only half the story. A key aspect of the story of the poor boy in Cologne is the fact that during much of the two-and-a-half years in which his cerebral ventricles enlarged, starting when he was seven months old, he ate, drank, spontaneously moved his limbs and looked around. Fabry’s conclusion that at the age of 2½ years he lacked not only speech but also hearing, sight and thought is probably only partly correct, but at least he could move. Near the time of his death – the report is not precise – he lapsed into a state of unresponsiveness (‘sopor’), but for much of the time his brain performed at least motor functions. And about the two-year-old girl in Augsburg Vesalius explicitly wrote that she “had the complete use of all her senses“ up to the time of death, although he does not provide illustrative details.

A second peculiarity is the mere fact that a post mortem study was performed, for which the children’s parents must have given their permission. As I discussed on page 18-19, it was an uncommon event that physicians dissected a body, at least with the aim of finding changes associated with disease and of understanding its causes. Such procedures were practically limited to judicial investigations or instances where the deceased was of high rank and the autopsy preceded embalming. In contrast, at medical schools dissection was a usual though infrequent practice, with the purpose of teaching students the structure of the human body. Fabry provided more examples of autopsy in his reports, for example the presence of abnormal material in the abdomen, or gross expansion of the liver and spleen,[145] but he was an exception.

Thirdly, Vesalius as well as Fabry enhanced the trustworthiness of their observations by asking other physicians to attend and perhaps to participate; the former only hints at their presence, but Fabry even recorded their names. This is an early example of a method to establish ‘matters of fact’ by engaging witnesses of appropriate social stature who confirmed new observations. This practice in medicine predates similar conventions with Robert Boyle’s experiments at the Royal Society by some sixty years.[146] What is more, Fabry made sure that some of the evidence could be shown to a wider circle and at a later moment in time: in the ‘Museum’ at his home he kept the bony part of the skull and a drawing showing the stunted growth of the patient’s body.[147] In those times proofs were important, since there was great general interest in stories and even books about miracles (Lycostenes’ chronological catalogue of prodigies and marvels was no exception).[148]

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145 *ibidem,* 203-205.

146 Shapin and Schaffer (1985), *Leviathan and the Air Pump*, 55-60.

147 There is a ‘Wilhelm Fabry Museum’ in Linden (https://www.wilhelm-fabry-museum.de/index.php); the descriptions of its contents do not suggest these items have made it from Cologne via Berne to Fabry’s home town.

148 Lycosthenes (1557), *Chronicon*.

The importance of brain tissue becomes textbook material

A few years after the Varolio-Mercurialis correspondence, the French-Swiss medical student ***Caspar Bauhinus*** or Gaspard Bauhin (1560-1634; see box) spent two years in Padua, between 1577 and 1579.[149] In the mean time Varolio had died; Mercurialis was still in function. Among the many books Bauhin would publish later in his career the best known is his textbook *Theatrum Anatomicum*, first published in 1605. The contents of this book makes it clear that the printed version of the letters from Varolio and Mercuriale must have come to Bauhin's attention – in his student days or later. He copied large sections of these texts, including Mercurialis' objections as well as the two woodcuts Varolio added to his text (figure 8 on page 43 is one of these). Bauhin mentioned Varolio in his book, but did not explicitly refer to him in the text or in the legend of the figures. He also included many other details of Varolio's argumentation than those I have cited, for example a section in which Varolio appeals to common sense in his proposal that the fluid in the ventricles represents waste products from the brain:

Gaspard Bauhin (1560-1634)

Gaspard Bauhin was the second son of the physician Jean Bauhin, born in Amiens in 1511. The father had studied in Paris under Fernel and Sylvius (Jacques Dubois) and became a successful practitioner in the French capital, until in 1532 persecution because of his protestant faith forced him to flee to England. On his return, three years later, he narrowly escaped death on the pyre, thanks to the intervention of the princesses he had treated. Eventually he settled in Basle, where Gaspard and his other children were born.

Gaspard also studied medicine, first in Basle, then in Padua (1577-1579) and another two years in Montpellier, after which he settled in his hometown in 1581. Apart from his medical practice, he taught anatomy and botany. In 1582 he also became professor of Greek at the University of Basle. Seven years later the same university appointed him to the chair of anatomy and botany and, finally, in 1614, to the chair of practical medicine as successor of Felix Platter. In 1623 he 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.

> If it were not collected in some quantity in some space, one would need to spit continuously (in the same way as people in whom there is no collection of urine [must] continuously void). In that case speech and other important actions would be impeded. In the same way we see that much phlegm is collected during sleep; afterwards we spit it out in great quantity, within a short time. Because this quantity cannot be entirely stored in the cavities of the nose, there was indeed a need for some cavity in the brain where it could be kept. Also 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 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.[150]

[149] Hirsch (1884-1888), *Biographisches Lexikon*, vol. VI, 460-461.

[150] Bauhinus (1605), *Theatrum Anatomicum*, 696 (corresponds with Varolio (1573), De Nervis Opticis 31r-31v).

Bauhin closes his paragraph on the ventricles of the brain by citing another appeal to common sense by Varolio, this time to bolster the point of view that spirits can be safely located in brain tissue. Spirits do not take up space, his argument goes; not even the nerves, in which they are eventually supposed to end up, have discernible channels. Therefore spirits do not require space either:

> Since animated spirit can flow and reflow without any discernible channel, why can we not therefore assign it to the substance of the brain, [only] because some people assign it to the ventricles, which have not been properly studied?[151]

Why did later authors so often cite Bauhinus rather than Varolio, though the former's points of view on the function of the ventricles were not original? Probably the answer is that Varolio's text must have had a modest circulation, in contrast to Bauhinus *Theatrum*, a textbook that became popular, given that it was reprinted in 1621.[152]

Apoplexy indeed described as unrelated to the ventricles

Felix Platter (1536-1614)

Felix Platter was born in Basle, where his father Thomas, a self-educated teacher of Latin, Greek and Hebrew, was a successful headmaster of the gymnasium, humanist, printer and publisher. In 1552 Felix departed on horseback to study medicine in Montpellier, accompanied by a friend. On his return, five years later, he travelled extensively in France before graduating in Basle and marrying Madlen Jekermann, daughter of a local surgeon. In 1562 he became professor of anatomy at the University of Basle, in 1571 city physician and professor of practical medicine. Like his father and his half-brother Thomas, Felix Platter kept an accurate diary.

The nemesis of the brain's ventricles, at least in the eyes of physicians who were aware of the observations of Varolio, Vesalius and Fabry, could not fail to affect the explanation of apoplexy. ***Felix Platerus*** or Platter (1536-1614; see box), appointed in 1571 as professor of practical medicine at the University of Basle, [153] must have heard about Varolio's work from his younger colleague Jean Bauhin, who would eventually succeed him in 1614. Indeed in a manual on anatomy Platter published in 1603,[154] the illustration of the base of the brain owes more to Varolius than to Vesalius. About apoplexy Platter wrote in his *Practica,* which appeared in three volumes between 1602 and 1608. Incidentally, he did not order diseases according to anatomical location, traditionally from head to heel (*a capite ad calcem*), but according to the symptoms, the manifestations of disease.[155] The first part was dedicated to disturbances of function, the second to pains and the third to deformities.

In the first part, on functional disturbances, Platter provides an introduction about the clinical features of apoplexy and related disorders, in agreement with the conventional, Galenic description; he also provides an explanation of the preservation of respiration ('partly natural, partly voluntary') and of the pulse (the heart acts independently from the brain). When he gives his view on what happens in apoplexy, it turns out that he has adopted

[151] *ibidem,* 698 (corresponds with Varolio (1573), *De Nervis Opticis,* 26v-27r).
[152] Poynter, ed. (1996), *Wellcome Catalogue,* vol. I, 39.
[153] The diaries of the Platters have been retold by an historian: Le Roy Ladurie (1995), *Le Mendiant et le Professeur*. The portrait of Felix is by Hans Bock The Elder (oil on linen, 227 x 156 cm, Kunstmuseum Basel).
[154] Platerus (1603), *De Corporis Humani*.
[155] Platerus (1602), *De Functionum Laesionibus*.

the Varolian interpretation that 'animated spirits' resided in the brain substance, not in the ventricles. In order to explain a sudden blockage of spirits, he suggests that the abnormal fluids directly affect brain tissue, either by inundation of its surface, followed by collapse, or at its base, through squashing of the spinal medulla (the part of the medulla lying within the skull is currently called the brain stem):

> 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 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 squashing the base of the brain in the same manner.[156]

This model of apoplexy, in which the dissolving brain is inundated by phlegm and, collapsing, squashes its own nerves, is based on speculation but also on two post mortem observations. Yet in both cases there is no clinical information, about symptoms and the course of the disease. The report of the first patient is quite vague:

> In some, copious fluid ran out as soon as the thick membrane of the brain had been opened by diligent dissection.[157]

One suspects that in fact there were few abnormalities, which may have created the same uneasiness that led Varolio to remain initially silent about patients with apoplexy and normal brains; in such an embarrassing situation it is not unusual to put the blame on 'copious' fluid. In the second example Platter gives a few more details about the changes in the brain, especially the version in a later book, with collected case histories:

> 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 cloths on both sides.[158]

I noted before that post mortem dissections were exceptional. However, Felix Platter is reputed to have been a champion of this procedure;[159] indeed he confesses having on one occasion secretly dissected, in the dead of night on the cemetery, the body of a phthisic boy with a perforated stomach.[160] Nevertheless, the above is the only example of such an observation about apoplexy in Platter's published writings. The report leaves several questions unanswered. First of all, the clinical features that led to the diagnosis of apoplexy are unknown; it is only in combination with symptoms and signs that findings on autopsy become reliable evidence.[161] Especially important is the time course of the disease: was the old lady in question healthy or at least in a stable physical condition beforehand and was the fatal disease indeed characterized by a sudden onset? If the brain tissue was indeed

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156 *ibidem,* 23-24.
157 *ibidem,* 24.
158 Platerus (1614), *Observationum Libri tres*, 14-15.
159 Buess (1964), 'Praktische Anatomie und Felix Platter'.
160 Platerus (1614), *Observationum Libri tres*, 407.
161 In current medical parlance, 'symptoms' are manifestations of disease experienced and voiced by the patients, 'signs' are phenomena observed by the physician, through inspection and physical examination.

'dissolved', one might perhaps think of an inflammatory disease, or of spontaneous decay owing to a long interval between her death and the autopsy; yet the length of this interval is also unknown. Moreover, the description of the abnormal texture of the brain is fairly general, whereas later reports would often distinguish between normal and abnormal parts of the brain, with regard to aspect or consistency.

Despite the many questions that remain about his two case reports, Platter at least leaves no doubt about his opinion that that he unequivocally located the site of apoplexy in the substance of the brain. I recall that ***Fernel*** had also reported, though incompletely, two patients in whom autopsy had shown a lesion at the base of the brain (page 39); on the other hand he still espoused the Galenic explanation of overstuffed ventricles.

Also causes outside the brain, through obstruction of blood vessels?

So far, the emphasis has been on causes of apoplexy *within* the brain, and how notions about such lesions gradually shifted from the ventricles to the brain substance. On the other hand, Fernel (see page 40), as well as others, entertained the theoretical possibility that vital spirits might fail to reach the brain, through obstruction of blood vessels, especially arteries.

In 1629 a monograph about apoplexy appeared in Wittenberg, a town in Sachsen-Anhalt made famous by Luther and situated halfway between Leipzig and Berlin. This was one year after the publication of William Harvey's book about the circulation of blood in Frankfurt, a theory that would gradually but completely change the thoughts about apoplexy. However, the author of the monograph, ***Gregor Niemann*** (Nymannus, 1592-1638; see box),[162] was blissfully unaware of the new theory during the long preparation of his text, followed by a delay at the printer. So I included his work in that of the pre-Harveian 'old guard'. Niemann was professor of medicine in Wittenberg, where he had in 1619 obtained his doctorate by a disputation on the same subject. He had a modern mind, in the sense that he felt that existing knowledge was incomplete and that each new generation should enlarge and supplement it. In the dedication of his book to the local greats of Saxony, he wrote:

> Someone entrusted with a sum of money who only hoarded it in a piece of cloth at home, instead of making a profit by business, is reproved and called a useless slave. We all deserve the same reproof if we are merely content with the art as it has been left to use by our Predecessors and do not add anything to it and strive to supply what is still missing to it. [....] So sooner or later we should take good care of the art of Medicine left to us by our Forefathers and also to add something by ourselves or, if some of it can be improved, to perfect it.[163]

Gregor Nymannus (1592-1638)

Aged two, Gregor Niemann lost his father Hieronymus, professor of medicine at the University of Wittenberg; he was raised by his mother Sibylla (née Strauch) as well as by his stepfather Tobias Tandler, physician and mathematician. Gregor studied philosophy and medicine in his hometown. Having obtained his licence as physician in 1618, he became doctor of medicine in the next year, following a disputation on the subject of apoplexy. He was subsequently appointed professor of botany in Wittenberg, at the age of 26 years. In 1626 he succeeded Wolfgang Schaller as the second professor of medicine, and in 1637 Daniel Sennert as the first. He had survived the plague in Wittenberg, but died a year later from 'a chronic disease of the spleen'. In 1628, a year before the appearance of the book *De apoplexia* as an expanded version of his doctoral thesis, he published *De vita foetus in utero*, in which he argued that when a pregnant woman died the child might be salvaged by caesarean section.

[162] Hirsch (1884-1888), *Biographisches Lexikon* volume IV, 395. Engraving by Lucas Kilian (1627).
[163] Nymannus (1629), *Tractatus de Apoplexia*, dedication iii-iv.

The channels at the back of the head

In his attempts to find a single site in the brain where obstruction might cause all the impressive symptoms occurring in apoplexy, Niemann argued as follows, after an extensive review and criticism of previous views about the subject and after paying his compliments to Varolio for his method of removing the brain as a whole from the skull:

> I confidently conclude that a very severe disease of such kind cannot evolve unless the vessels and channels that carry the vital spirit and distribute it through the brain are occluded, ... [164]

And he continued:

> At the end of the day, however, when I looked into the matter a little deeper and carefully contemplated the vessels of the brain one by one, I came upon a site, which I have shown in all my public and private dissections, before the time when I first proposed this, ten years ago, as well as afterwards up to now. From this site blood and spirit are distributed to the brain like from a wellspring; by its occlusion the brain can be at once deprived if not from all, at least from most of its spirits. This is the confluence of all sinuses of the thick membrane (which some people have called the Wine press or *Torcular*, because blood from veins and arteries that has flowed to those channels is pressed into the entire substance of the brain, like from a wine press); [it is] prominent in the posterior region of the brain, near the top of the lambdoid suture, where the fourth and third sinus take their origin, where also the two first [sinuses] join.[165]

Let me explain here that Niemann's reasoning critically depends on a traditional, pre-Harveian picture of the movement of blood. Although arteries and veins were distinguished according to differences in the structure of their walls, blood was thought to move more or less to and fro, depending on the needs of the organs to which the vessels were connected. The ***sinuses*** about which Niemann speaks are vessels of another type; their structure fails to resemble that of either arteries or vessels. In the schematic drawing below (figure 11) the sinuses have been given a blue colour, because they are now known as part of the venous system in a functional sense: they are part of the vessel structures transporting blood from the brain back to the heart. The sinuses form the link between the countless small veins draining brain tissue that end up in them (not shown in the figure) and the jugular veins in the neck, which are also 'proper' veins. The anomaly in the structure of the sinuses is that they are not built as tubes, but as duplicatures of the *dura mater*, the hard membrane surrounding the brain as a whole as well as some of its parts.

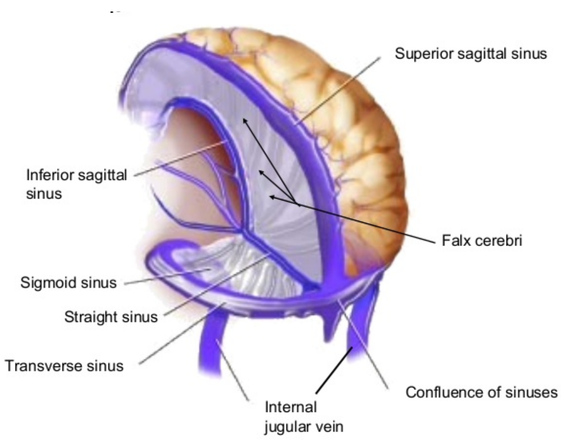

Figure 11. *The* sinuses *of the brain. The front of the head is at the left side of this drawing, the back at the right. The* dura mater *(hard membrane) primarily envelops the entire brain (not shown) but also forms two membranes separating parts of the brain (shown in grey colour). One is the* tentorium *(tent), shown on the left side only, between the brain and the cerebellum (below). At its side it splits in two and forms the transverse* sinus *on the left and right. The other separation is the* falx *(sickle) between the right and left half of the brain. At its top it is also split in two and so forms the third* sinus *(modern name: superior sagittal sinus). The fourth* sinus *(modern name: straight sinus) is formed where the* falx *and the* tentorium *meet.*

[164] *ibidem,* 96.
[165] *ibidem,* 103.

Niemann supposed that the *sinuses* transport blood towards the brain, instead of leading it away from it. He therefore regarded the point were the four main sinuses converge, now still called the *torcular* or wine press,[166] as the site where blood was distributed to all parts of the brain. As a consequence he supposes that obstruction at this point, for which he presents some evidence, might prevent access of spirits to the brain and so cause apoplexy:

> It can easily happen that this is occluded; indeed also in some cadavers after a violent death I found around this region a thick sanguineous fluid, often also mixed with viscous phlegm, solidified and quite compact, very suitable for obstructing it.[167] [....] I advise all who at some time open the heads of Apoplectics to pay meticulous attention to this site and to give proper consideration to the fluids around it; surely they will find there quite thick and sticky material... [By this obstruction] no blood or spirits can be discharged into the third and fourth sinus; the brain, bereft from the largest supply of spirits, is deprived of all its functions and without doubt Apoplexy follows.[168]

It is important to note that Niemann cites evidence from autopsies here, but the comment is rather casual; I do not know of any report of his with full details, that is, clinical features in conjunction with anatomical findings such as the 'viscous phlegm'.[169] With regard to other possibly obstructive substances, he later mentions black bile and blood clots.[170] Be that as is it may, he apparently regards obstruction of the *torcular* as insufficient in itself to explain the full-blown apoplectic syndrome, for he goes on to present apoplexy as a two-stage process:

> No small contribution to this occlusion of vessels and channels is also made by the collapse of the brain. For since this organ is vaulted over and is characterised by certain arches and, as long as it is enriched and made light by the vital spirits, [it is] extended and stretched; its cavities are dilated and much larger than they appear in the dead. However, as soon as the source of spirits is closed off, and the point of confluence of all sinuses is occluded, having been despoiled of the greatest part of the spirits that sustained it, [the brain] does not have the intrinsic power exerted by the spirits and it collapses; once collapsed, it compresses not only the cavities and pores, but also the channels of the vessels, including the lower cervical arteries that are otherwise hiding below its base. By compressing the [cervical arteries] it occludes them to such an extent that, if they were not [already] obstructed by the excess of fluids, they would finally still be compressed by the sagging mass of the brain and, having been compressed, they would deny all transit of vital spirits to the brain.
>
> From all this it is clear that in the first place by an obstructed and occluded confluence of sinuses, as the primary cause, and in the second place, subsequently and depending on this, by sagging of the brain, which in my opinion always takes place as well, as the secondary cause, all sense and mental actions are arrested and abolished in Apoplectics.[171]

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166 The *torcular* is named after the Greek physician Herophilus (335-280 BC), who lived in Alexandria and is believed to have performed autopsies. A wine press would consist of a shallow basin (Roman times) or a barrel (16th century), with a variety of methods, such as screws, to exert pressure on the grapes. Some presses had more than one spout at the bottom; this led to the analogy with the sinuses, in that pressure at the point of confluence might force blood into the various channels.

167 Nymannus (1629), *Tractatus de Apoplexia*, 103.

168 *ibidem,* 104.

169 Retrograde diagnosis is a hazardous undertaking, but I cannot refrain from commenting that purulent inflammation extending to the transverse sinus was a common complication of ear infections. These could surely lead to a kind of 'apoplectic state' and eventually be fatal, but would rarely have a sudden onset.

170 Nymannus (1629), *Tractatus de Apoplexia*, 120-128.

171 *ibidem,* 105-106.

The model of the 'sagging brain' is reminiscent of Platter's explanation, but while the latter envisaged a drenched brain compressing its own nerves and denying access to spirits, Niemann assumes a lack of spirits as the primary event; they do not only have a signalling function, exerted via nerves, but they are also supposed to keep up the scaffolding of the brain, as gases with a balloon. Interestingly, in order to bolster his point of view Niemann adduces a clinical observation that has not been confirmed by others:

> This opinion of mine is in keeping with the swelling of the jugular vessels in the neck of Apoplectics. When these cannot discharge themselves into the sinuses of the brain, the blood and spirits contained in them go back and distend and inflate them. If, however, only the nerves were barricaded, as the common opinion of Physicians has it, and the other vessels of the brain would not at all be occluded, [....] blood and spirit would still be poured into them, and no cause could be given for this dilatation.[172]

This is a nice example of Fleck's 'Gestaltsehen': apparently a chance observation is generalised and used to support an emerging theory, while contrasting observations are neglected.[173] To complete the picture I should mention that Niemann distinguished a spurious form of apoplexy, in which collapse of the brain occurred without preceding blockage at the *torcular*, a form that in his view could be caused by an excess of serum.[174]

The fluids thought to cause obstruction and apoplexy

Another aspect of apoplexy that has often divided opinions is the substance responsible for the obstruction, wherever it occurred.

Phlegm

Earlier on I cited a passage by ***Fernel*** in which he wrote how phlegm could cause apoplexy by filling the ventricles. In fact he regarded phlegm as the only cause at that location:

> [The cause] is in fact 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.[175]

Several later authors criticized Fernel for regarding phlegm as the only substance capable of causing apoplexy by filling the ventricles; they included both black bile and blood as a possible material causing obstruction inside the brain. An example is ***Forestus*** (Pieter van Foreest; 1621- 1691), to whom I will come back later. If he thinks the cause of apoplexy is obstruction within the brain, Forestus, describing the consistency of the fluid as fat, thick, viscous or bilious,[176] derives the origin of the fluid from circumstantial evidence: phlegm if the apoplectic attack occurred in someone with a pale complexion or during cold weather, an excess of blood in a plethoric person, or black bile in a person with a melancholic disposition.[177] Since the ancient authors had never incriminated yellow bile, the fourth of the Hippocratic humours, none of the 16th-century physicians whose work I consulted attributed a role to it in relation to apoplexy.

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172 *ibidem,* 107.

173 Fleck (1980 [1935]), *Entstehung einer Tatsache*, 121.

174 Nymannus (1629), *Tractatus de Apoplexia*, 129-134.

175 Fernelius (1554), *Medicina* (Pathologia), 133.

176 Forestus (1653 [1590]), *Observationes et Curationes,* volume X, 508 L column. Apart from an excess of a particular humour ('disorder of composition') Forestus, taking this lead from Avicenna, also assumed 'disorders of disposition' as possible causes, such as inflammation or a tumour.

177 *ibidem,* 514 R column-515 L column.

Blood

As indicated above, ***Fernel*** restricted the role of blood to obstruction at the base of the brain. In contrast, ***Platter*** 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:

> Blood ... suddenly filling the ventricles and the convolutions may obstruct and compress the beginning of the nerves and it causes stupor and apoplexy...... Up to now I have so often seen a large haemorrhage emerge through the mouth and nose, in the living as well as after death, that I have persuaded myself more than once that this is the most important cause of apoplexy.[178]

It is now known that loss of blood through the mouth or nose in an unconscious patient is always the result of trauma by some external force, so that this argument of Platter must have been derived from accidental causes and it cannot help us to understand the 16th-century explanation of 'spontaneous apoplexy'.

Petrus Salius Diversus from Faenza, who had been trained as physician in Naples and practised in his hometown during the second half of the 16th century, thought the recognition of blood as a cause of apoplexy was important for the choice of treatment.[179] In his monograph on the plague he added a few chapters on the treatment of diseases that in his view had received insufficient attention, including apoplexy. Though recognising phlegm and black bile as possible sources of obstruction, Salius saw apoplexy by excess of blood as overfilling of all vessels and subsequent compression of their pathways, instead of actually filling of the ventricles, which in his view would lead to clotting and sudden death. The usual measures for apoplexy through excess of cold fluids were usually aimed at warming the head, which would be disastrous in sanguineous apoplexy.[180]

The surgeon ***Wilhelm Fabry*** contributed not only, as I recounted above, one of the two early case reports on infantile hydrocephalus, but also a curious history in which an abundance of blood was regarded as the cause of apoplexy, though only by implication: in a patient with apoplexy who had earlier on obtained a miraculous cure for the recurrent nosebleeds from which he used to suffer, an excess of blood must surely have been the cause – at least this is how the reasoning goes:

> *Simon Clericus*, goldsmith in Lausanne, of French extraction, a pious, sanguine and robust man, was susceptible to nosebleeds from a young age onwards. Though on each occasion a few ounces of blood flowed out, every one or two years it again erupted with such force that it could only be stopped with difficulty. I have seen this with my own eyes when in the year 1586 the blood flowed so impetuously and copiously from his nose that his life was in danger. I was called in consultation together with the late *Jacobus Aubertus Vindo,* very learned and for a long time very famous Doctor of Medicine for the community of Lausanne, whom I should very much honour as a friend and patron. We restrained the outflow of blood in him, with much trouble and many efforts. Nevertheless he recovered with divine help, and lived on for a few years. Yet, wary of the danger of the repeated haemorrhages from the nose, and having prevented the bleed by some amulet he had hung round his neck, he was seized by Apoplexy in the year 1589.[181]

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[178] Platerus (1602), *De Functionum Laesionibus*, 27.
[179] Hirsch (1884-1888), *Biographisches Lexikon* volume II, 192.
[180] Diversus (1584), *De Febre Pestilenti Tractatus et Curationes Particularium Morborum*, 227 and 229.
[181] Fabricius (1641), *Centuriae*, 356.

In the same way apoplexy in postmenopausal women could be attributed to overfilling of blood vessels (plethora) following the cessation of menstrual blood loss.[182]

Black bile

That under some circumstances also accumulation of black bile or *melancholy* could give rise to apoplexy was received knowledge – Fernel being an exception. ***Hieronymus Cardanus*** (Girolamo Cardano, 1501-1596), philosopher, physician, astronomer and mathematician, for some time teacher in Padua but often moving around because of his great talent for making enemies,[183] postulated that practically *all* cases of apoplexy are caused by black bile.

> I say that no apoplexy occurs because of phlegm; I add that all cases of apoplexy occur because of black bile. When I say none or all, I mean in a medical, not in a mathematical sense, for I should not deny that out of a hundred cases one or two occur from phlegm. My proof is the following. The most calamitous diseases arise from unconquered and worst humours; black bile is the worst, and apoplexy is the most calamitous disease. Furthermore in infants the brain is full of phlegm, like at no other age; yet is has never been observed that an infant is seized by apoplexy, although very many of them are susceptible to epilepsy. Finally, if apoplexy arose mainly by phlegm, especially aged people whose brain abounded with phlegm would be seized by it, so that they would usually suffer from headaches and hoarseness; also they would drink water rather than wine, and be drowsy rather than alert. None of this is the case: for the disease strikes wine-lovers, people who are active and alert, with a head that is fleshy, not dripping with phlegm from the nose or the palate.[184]

Serum

Cardano had few partisans, but things would turn out differently in the case of ***Carolus Piso***, or Charles le Pois (1563-1633; see box), who implicated serum.[185] Of course serum was not one of the four Hippocratic humours, but it was well known that if blood obtained by venesection is left standing in a glass or cup, it would soon form a clot, leaving a layer of clear fluid, serum, above it. So serum was regarded as a component of blood. In a monograph Le Pois published in 1618, he highlighted the role of serum in the pathogenesis of several diseases. In this fashion he proposed that serum might explain several features of apoplexy, a point of view that would produce many echoes in later generations, as far ahead as the beginning of the 19th century. His first argument is the rapidity with which in 'mild' cases of apoplexy the manifestations change, when a sudden episode of prostration is followed by paralysis of one side of the body:

Charles le Pois (1563-1633)

Charles le Pois was born in Nancy, where his father was physician of the count of Lorraine. Having studied medicine in Paris and Padua, he started a practice in his hometown, until he also became physician to the count – first Charles III, then Henri II. In 1598 he became dean and professor of medicine at the newly founded university of Pont-à-Mousson (Lorraine), which was intended as a Jesuit bulwark against the Protestantism beyond the eastern border.

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182 Stolberg (1999), 'Medical perceptions of menopause', 410.
183 Siraisi (2015), *Girolamo Cardano*.
184 Cardanus (1564), *Aphorismorum Hippocratis Commentaria*, 727.
185 Saucerotte (1854), *Charles Le Pois*.

> Though I agree with all Physicians on the issue that a thick and viscous fluid of either phlegm or black bile (which itself is a thick excrement of blood) can cause apoplexy and sudden falling by obstructed or compressed cavities of the brain, I will admit this only for strong apoplexy. That I feel differently about mild apoplexy, which usually changes into paraplegia or hemiplegia, is because I am convinced by that manner of the weakness, to wit, the immobility of the entire body or half of it. For how can viscous fluid, by its toughness sticking to the wall of the ventricles of the brain like firm glue, within a moment be almost wiped off, driven out and forced into the beginning of nerves? How can thick and overall glutinous fluid steal into the hollow parts of nerves,[186] so narrow that they escape the eye, let alone run along their length to the fibres with the same speed as that change [of the symptoms]?[187]

It is clear that Le Pois was still a firm believer in obstruction of the cerebral ventricles as a cause of apoplexy. The issue of hemiplegia as a clinical feature of apoplexy is a point I shall come back to, but the point is here that Le Pois explains it as a change in the location of the obstructing fluid, from the brain to the nerves of the affected side; such a quick change is improbable in case of thick phlegm, he reasons. In addition, he refers to the gradual improvement of movements and sensation in the paralysed limbs on one side.

> Finally, how can that same superfluous fluid be entirely and completely cleared? For paralysis is never replaced by another disease, but it is gradually alleviated, though not completely, but to some extent, so that within a few months – or even days – the body is restored to its former sensation and motion. How can, I say, thick fluid be completely cleared, since complete clearance of fluid can be achieved only by the force of heat, whereas thick and tenacious fluid is likely to become more and more encrusted and solid by heat, as is known from natural philosophy and from stones formed in the bodies of animals by this kind of fluids, as well as from crusts in the nose by the collection of hardened excrements of the brain? If these things are true – and they are as true as can be – it is my opinion that the conjoined cause of mild and persistent Apoplexy is a collection of serum in the brain.[188]

Contributory factors

To close the discussion of causes in what might with some imprecision be called the 'era of the ventricles', it is appropriate to hitch on to Le Pois' term 'conjoined cause' (*causa coniuncta*), by which he probably means 'efficient', 'immediate' 'proximate' or 'direct' cause. All authors I cited so far were almost without exception aware that the causal chain of events is more complex than just the last phase. In other words, though patients might have a constitution predisposing them to an excess of phlegm, blood or black bile, almost invariably authors also mentioned more 'intermediate', 'distant' or 'remote' causes in the form of external factors that were thought to have precipitated the apoplectic event.[189] I have all but passed over this subject until now, but the factors most often implicated deserve to be mentioned briefly. Factors implicated for apoplexy of any type are advanced age and a short and narrow neck; if phlegm was regarded as the efficient cause, remote causes that receive mention include cold weather, cold drinks, viscous food, frequent wine drinking, long sleep and suppression of excretions from the nose and mouth. In case of

186 The notion that nerves have invisible cavities along their length is implicitly assumed by ancient sources as well as by authors in early modern times; le Pois is among the few writers to state this explicitly.

187 Piso (1618), *De Praetervisis hactenus Morbis*, 89-90.

188 *ibidem,* 90.

189 Some authors systematically list them, for example Saxonia (1639), *Opera Practica*, 38 R column-39 L column.

sanguineous apoplexy strong emotions, physical exertion and excessive sexual intercourse are often incriminated. It is perhaps needless to add that these relationships were founded on theoretical presuppositions rather than on actual observations.

Additions to the diagnostic 'frame' of apoplexy

In the introduction to this thesis I intimated (page 4) that medical diagnoses do not represent ontological unities but are largely changeable conventions, shaped by physicians and determined by phenomenological, material and socio-cultural factors. Apoplexy is no exception. Also in the 75 years between 1550 and 1625, some refinements have been added to the initial, simple notion of apoplexy: a sudden fall, accompanied by complete loss of sensation an motion, with preservation of respiration and heart action. It is necessary to pay attention to these small changes in the medical perception of apoplexy, if only because some of them, especially hemiplegia, were part of ideas about causality.

Hemiplegia

Several physicians noticed that apoplexy was often followed by paralysis on one side of the body. This was already apparent in Lycosthenes' story about his own disease (page 33); in fact according to his account he was aware of the right-sided paralysis almost from the beginning. This prompts the question – not explicitly addressed by any author in the period covered in this chapter – whether the selective paralysis of the arm and leg on one side might not actually be present at the very onset of the disease but cannot be recognised by physicians or companions because the patient is mute and 'senseless'.

Jean Fernel, in the part of pathology of his textbook *Medicina*, begins with a definition of apoplexy that contains the well-known cardinal features. He then uses the phenomenon of paralysis as a means to distinguish apoplexy from *carus*, one of the other forms of mental obtundation that were distinguished at the time:

> "For although in carus and in every [case of] severe sleepiness the foremost parts of the brain are compressed and the senses departing from there become numbed, the posterior parts are still intact and pour sufficient spirits into the nerves; thereby movement is spared, most of all that of respiration, which is primarily needed for the conservation of life. But apoplexy occupies and disturbs everything, takes away every movement and respiration and mainly through that cause kills a person. In addition, good health awaits a person with cured *carus*; [after] apoplexy it is paralysis."[190]

I pass over Fernel's opinion about the localisation of functions in the brain - a subject with its own history and literature.

Petrus Salius Diversus (second half of the 16th century), whom I cited before (page 58) because of his insistence that treatment of apoplexy by an excess of blood (within its vessels, he thought) had to be different from the management of apoplexy by cold humours, attributed paralysis of one side of the body to displacement of morbid material from the brain to the nerves, where it would get stuck.[191] We encountered a similar explanation in the work of ***Carolus Piso*** (page 59).

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[190] Fernelius (1554), *Medicina* (Pathologia), 133.

[191] Diversus (1584), *De Febre Pestilenti Tractatus et Curationes Particularium Morborum*, 234-235.

An authoritative medical writer was ***Petrus Forestus*** or Pieter van Foreest (1521-1597).[192] In Book X of his *Observationes et Curationes*, dedicated to diseases of the brain and its membranes, first published in 1590, he included fourteen sections with case histories of apoplexy.[193] Each section refers to one or more patients, though some of the stories are very brief. In the ensuing *scholia* certain points are highlighted, with some attempts at organizing the text. For example, the comments after the first case report, entitled 'About apoplexy', include general issues such as nomenclature and clinical features. Other sections have titles such as 'About some people with a humid constitution and sensitivity to southern winds, seized by apoplexy', 'apoplexy followed by sudden death', or 'phlegmatic apoplexy'. Accordingly, most of the information is scattered throughout the text of the different observations. Where opinions of others seem to differ from each other, Forestus often tries to reconcile them into a single model; sometimes he leaves the decision to the reader, and wherever he makes a choice he does this unobtrusively, without throwing in the weight of his authority.[194] Therefore he seems to fit into the category of 'aggregating' authors, influenced by scholasticism as well as humanism, who tried to arrive at a coherent picture by combining established wisdom with new knowledge.[195]

To return to the subject of hemiplegia, it did not escape

Pieter van Foreest (1521-1597)

Later generations have called Pieter van Foreest 'the Dutch Hippocrates'. He was the third child of a wealthy couple in Alkmaar, where his father served in several public offices. After secondary school he studied liberal arts and medicine in Louvain (1536-1539). This was followed by a tour of medical faculties in Northern Italy; he graduated in 1543 in Bologna, but also spent time in Venice, Ferrara and Padua. After an eventful journey on foot to Rome with botanists (1545) he visited Paris and Orléans, but the next year he was back in Alkmaar, where he married Eva van Teylingen.

In the course of twelve years Van Foreest established a solid reputation as physician in Alkmaar. He then accepted the post of city physician in Delft, where the plague was raging. He would stay there 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 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, aged 74, decided to return to Alkmaar, again as city physician. Meanwhile he had started to publish, from 1584 onwards, selected case histories of patients, usually together with the treatments he had applied. After each case history Forestus added comments (*Scholia*), to highlight certain features the views of other authors, ancient or contemporary. These *Observationes et Curationes Medicinales* were systematically organized: the first seven books were on different kinds of fevers, a subject that could not be attributed to a specific part of the body; thereafter each book dealt with a specific organ or body part, from the head down; each published volume contained one to three books. In 1597, the year Van Foreest died, the series had progressed to books 26 and 27. The publications continued post-humously; the last book (32), on syphilis, appeared in 1606. But that was not the end; in 1610 and 1611 two volumes with nine books of surgical observations appeared. The medical and surgical observations were reprinted together as *Opera Omnia*, in several editions between 1619 and 1661.

[192] Bosman-Jelgersma (1996), 'De Levensloop', 6-16. The engraving in the box is by unknown artist after Goltzius, made between 1585 and 1600; 132x81 mm, Rijksmuseum, Amsterdam.
[193] Breugelmans and Gnirrep (1997), 'Bibliografie', 17-116.
[194] Forestus (1653 [1590]), *Observationes et Curationes,* volume X, 505-533.
[195] French (1985), 'Berengario', 63.

Forestus' attention that patients who survived apoplexy were often left with paralysis of the arm and leg on one side.[196] Forestus assumed that if hemiplegia occurred the collection of thick material was less abundant, citing Benedictus Faventinus, his teacher in Bologna.[197] Some patients, he reported, were eventually able to walk again;[198] one of them even survived for 12 years after the attack.[199]

In the case of a young patient with apoplexy, occurring in the middle of the 80-year war in which Dutch Protestants sought independence from the Catholic King of Spain, Forestus noted an unusual feature.

Failure of speech

In this young patient the hemiplegia that 'followed' was accompanied by a problem with speech:

> 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,[200] together with Mr. de Bossu. In the early 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. At this time he stayed in The Hague.[201]

As other physicians of his time, Forestus called the difficulty with speech 'impairment of the tongue'; in other words, he regarded it purely as a problem of motion, or paralysis. But there was also, he noted, a problem of comprehension. Although he must have had some inkling that the difficulty in understanding resulted from dysfunction of the brain, or 'the senses', he did not elaborate this point. Nowadays the production as well as the comprehension of speech is located in the brain (in the frontal and temporal lobe, respectively, most often on the left side).

Respiration

Forestus regarded the preservation of breathing while other movements were suspended as an important feature of apoplexy, though its explanation continued to puzzle physicians; a common explanation was that it was 'a movement of nature, not of the will'. Forestus followed Galen in distinguishing four types of respiration in apoplectic patients, with increasingly small hopes of survival. In the worst type (grade 1), with irregular and forceful inspiration, death is imminent. If respiration is variable in frequency as well as in depth (grade 2), death is to be expected, but not immediately. In grade 3 breathing is irregular, but not violent; the patient may survive. If breathing occurs with regular intervals and with sufficient depth, the patient should survive with proper care.[202]

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[196] Forestus (1653 [1590]), *Observationes et Curationes,* volume X, 517-518 and 526, L column.

[197] *ibidem,* 519, L column. Benedetto Vittori (from Faënza; 1481-1561) taught in Padua (1534-1540) and Bologna (1540-1561).

[198] *ibidem,* 520, L column.

[199] *ibidem,* 529, L column.

[200] Count de Bossu, from the Southern Netherlands, admiral of the Spanish fleet, was defeated by the protestant troops at the battle of the Zuiderzee, in 1573; de Bossu was detained for 3 years in the orphanage of Hoorn.

[201] Forestus (1653 [1590]), *Observationes et Curationes,* volume X, 526, L column.

[202] *ibidem,* 510, R column.

Sputum around the mouth
Many authors mention that frothy sputum around the mouth of the patient is an ominous sign with regard to outcome; the sign goes back to the Aphorisms of Hippocrates.[203] But ***Hercules Saxonia*** (1551-1607), professor of practical medicine in Padua from 1575 onwards, distinguished two kinds of sputum: if the frothy scum consists of thick sputum with bubbles from exhalation, patients may recover; but if it is made up of lung tissue liquefied by heat, with bubbles from enclosed vital spirit, no hope is left.[204]

Apoplectic or dead?
For the detection of barely perceptible respiration many authors describe measures 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.[205] Similarly, Forestus warned that feeling the pulse can be treacherous, as illustrated by stories of patients who were about to be buried but miraculously recovered; hence the statutory delay of three days between apparent death from apoplexy and burial;[206] this precaution is a recurring item in almost every essay on the subject, from widely different parts of Europe.

Distinction from other conditions with decreased level of consciousness
Physicians had to distinguish apoplexy from other conditions in which the senses are benumbed, sometimes with sudden onset. Fernel had distinguished it from *carus* (above, page 61), while Forestus also mentioned sopor, lethargy, catalepsy, epilepsy, paralysis, syncope and suffocation by the uterus.[207] He stipulated that the distinction between these states, a subject I have to forgo, could be difficult if the patient had already died by the time the doctor arrived. An example was the sudden death of a certain Hugo Grotius; Forestus stressed the fact that eyewitnesses had not observed any signs of breathing or of fluid emerging from the patient's mouth, so he concluded the cause of death was not apoplexy but syncope, a sudden cessation of heart action through loss of 'innate heat'.[208]

Treatment

I cannot avoid dedicating a small section to treatment, a subject I promised to leave largely alone. The reason is not only that the rationality of the therapeutic measures is often difficult to understand; an immense variety of botanical concoctions intended to drive the harmful substance from the body was usually supplemented with an almost standard repertoire of interventions intended to remove fluids from the stomach, the bowels or the blood vessels. In fact the interventions were a direct consequence of the ideas about causation that are the true subject of the present study.

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[203] Hippocrates (1939), *Genuine Works*, ed. Adams, 305. Aphorism II: 43 reads: "Of persons who have been suspended by the neck, and are in a state of insensibility, but not quite dead, those do not recover who have foam at the mouth."
[204] Saxonia (1639), *Opera Practica*, 39.
[205] Forestus (1653 [1590]), *Observationes et Curationes,* volume X, 513, R column.
[206] ibidem, 529, L column.
[207] *ibidem,* 514. 'Suffocation by the uterus' was, of course, a condition occurring only in women. The term was used to describe a kind of swooning, attributed to vapours arising from the womb.
[208] *ibidem,* 513-514, L column. The patient in question is not the famous lawyer Hugo Grotius (1583-1645), perhaps his uncle.

Yet, common expressions such as 'proper care' leave no doubt that physicians in general were convinced of the adequacy of their ministrations. These were based not only theory but sometimes also by fortuitous outcomes in similar situations before. Therefore I might at least give an impression, by summarising the treatment received by the melancholical young man who suffered from an apoplectic attack with hemiplegia on the right and difficulty with speaking and understanding speech during a stay in The Hague (above; page 63). The description of his case by Petrus Forestus took up about a thousand words, three quarters of which are devoted to treatment.

In order to dissolve and drive away the thick fluid in the brain, in this case supposed to be black bile (given the patient's melancholical disposition), the young officer was subjected to enemas, venesection (where best to apply this was the subject of a separate discourse between physicians), administration of elaborate mixtures of herbal extracts, rubbings of the paralysed limbs, gargling solutions and restriction of food. The patient's hostess in The Hague, Mrs. Van Cloetingen, had observed that his speech improved if a leaf of peony was put under his tongue.[209] The regimen was continued with many more rubbings and drugs. The purpose of all these interventions was to dissolve and drive away the excess of thick fluid from the brain. Eventually an almost complete cure would have resulted, according to Forestus, but it is uncertain how long this recovery took.

Back to causes of apoplexy: the movement of blood

After these brief excursions to the clinical syndrome constituting and to some of the methods of treatment physicians applied, I would like to return to a further discussion of the development of ideas about the causal factors of this disease. However, with regard to apoplexy as well as many other diseases the period between 1550 and 1700 has to be split in two halves, separated by the theory of the circulation of blood. That I have so far hardly paid attention to medical opinions about the movement of blood is because these did not directly affect the interpretation of apoplexy, apart from the notion that vital spirits had to be transported by blood to the brain. This would change profoundly – though slowly – after the first quarter of the 17th century: once physicians accepted the notion that blood was pumped round and round in the body, this finding had grave implications for subsequent views on the events in the brain that caused apoplexy.

It is for this reason that I have intercalated a separate chapter on the movement of blood between the two chapters covering the development of pathophysiological insights into apoplexy before recounting the developments after 1625.

[209] *ibidem,* volume X, 526, L column.

Chapter 5

THE MOVEMENT OF BLOOD

Galen about the movement of blood

William Harvey's theory of circulation

René Descartes and the circulation of blood

Before describing the changes that occurred in the ideas about the movement of blood, I wish to give an impression of the commonly accepted notions before that time. These were mainly based on Galen's work.

Galen about the movement of blood

As is the case with Galen's writings about brain function and apoplexy, the ambiguity or even contradictions in the wording of his views has led to diverging interpretations; some authors even contend that he would have been aware of the principle of circulation, as discussed elsewhere in detail.[210] With regard to anatomy, Galen had made important observations: he was aware of the structure and function of the four valves in the heart, he supposed there were some connections between the terminal ramifications of arteries and veins,[211] and he found, other than his long-term predecessor Erasistratus, whom he often criticised, that arteries transported not just air but also blood.[212]

Despite these observations with regard to structure, Galen based his functional interpretation of the vascular system on four assumptions that have not withstood the test of time. The first was the notion that air from the lungs enters the left chamber of the heart, via a large vessel, the 'vein-like artery' (figure 12).[213] In Galen's model, air and blood are thought to be mixed in the heart, in order to produce the 'vital spirits'; but since blood cannot arrive in the left chamber via vessels, it passes from the right chamber, via invisible pores in the wall (*septum*) between the two parts of the heart.[214] The right ventricle provides nutrition and cooling to the lungs, while the left ventricle feeds especially muscles.

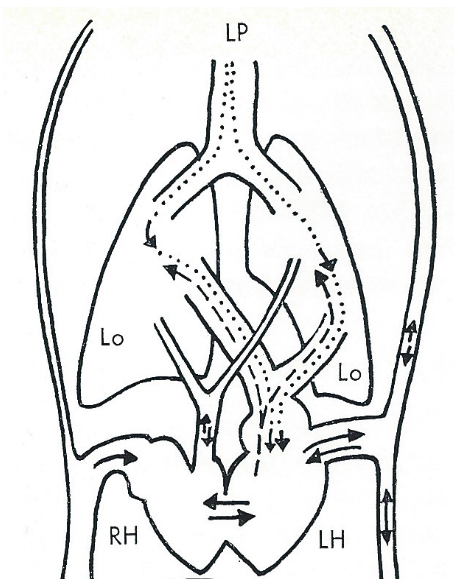

Figure 12. *Directions of blood and air in the chest, according to Galen. LP = windpipe, Lo = lungs, RH and LH = right and left chamber of the heart. After Van den Berg.*

Secondly, Galen situated the origin of all veins in the liver, where all blood is produced, after preliminary digestion by the stomach and bowels. Via these veins the liver supplies blood to all the abdominal organs and even to the diaphragm and lower part of the chest.[215]

Thirdly, all blood transported from the two centres, the heart and the liver, is consumed in the periphery by organs and muscles. All that remains is waste material: 'soot', going from the left chamber to the lungs along the same way as the incoming air; black bile is carried to the spleen, yellow bile to the large

210 Harris (1973), *The Heart*, 310-322; Pagel (1967), *Harvey's Biological Ideas*, 133-135.
211 Harris (1973), *The Heart*, 364.
212 *ibidem,* 278.
213 Herophilus (c. 325-c. 285 BCE) introduced the convention to call all vessels connected to the right half of the heart 'veins' and those connected to the left half 'arteries'. He recognised that most arteries had a thicker wall than veins; to solve the problem that the large vessels between the lungs an the heart did not fit into this morphological pattern, the vessel between the lungs and the left ventricle was called the 'vein-like artery', and the vessel between the lungs and the right ventricle the 'artery-like vein' (*ibidem,* 179*).*
214 *ibidem,* 283, 305, 308 and 335.
215 *ibidem,* 325-329.

('hollow') abdominal vein or the gall bladder,[216] and of course superfluous fluids are excreted via the kidneys.

The fourth problem is the 'hydrodynamic' aspect of the movement of blood. Galen only partly uses mechanical explanations, such as heaviness and '*horror vacui*': in the same way as suction through a straw replaces air by fluid, the left chamber of the heart sucks air from the lungs via the 'vein-like artery' in the expansion phase of heart action. But a substantial part of the force moving the blood in the Galenic model is defined not in a physical but in a teleological sense: the need of each organ to withdraw specific structural components from blood.[217] In this view it is the balance between supply and demand that determines the direction of the blood flow in many vessels; unavoidably this implies to some extent a to-and-fro movement (figure 12),[218] or even two-way traffic.[219]

William Harvey's theory of circulation

Often a discovery – as Harvey's theory is called from a current point of view – is not just a bolt from the blue but is it possible to identify contributory factors, at least potentially. The notion of circularity has always had attractions for natural philosophers, for example in the well-worn analogy between macrocosm and microcosm.[220] William Harvey himself (see box) cites Aristotle as a source of inspiration.[221] Also Harvey may have been stimulated by a few earlier investigators who had established, largely independently from each other, that the septum of the heart is impermeable and that blood is forced from the right lower chamber (ventricle) of the heart into the lungs, where it is mixed with air, and subsequently returns to the left ventricle. The first was Ibn-al-Nafis from Damascus (13th century),[222] followed by Michael Servetus (1511-1553) and Realdo Colombo (1515-1559).[223] Finally Andrea Cesalpino (1525-1603) had argued that the liver should be dethroned as the source of all veins.[224]

William Harvey (1578-1657)

Harvey was the eldest son of a merchant and landowner in Folkestone. He went to a grammar school in Canterbury and received a bursary to study medicine in Canterbury. In 1599 he left Canterbury for further studies in Padua, where he obtained a doctorate after three years. Having started as a private practitioner in London on his return, he subsequently received appointments on the staff of St. Bartholomew's Hospital (1609), as lecturer in anatomy at the Royal College of Physicians (1615) and as physician to the king (at first James I, after 1625 Charles I, for whom he also carried out diplomatic missions). He followed king Charles on his flight between 1642 and 1646; during the reign of the protestant republicans he could resume his anatomical teaching, but his political role had ended. He died before the restoration of the monarchy in 1660. Apart from his famous book about the circulation (1628), Harvey also published a book on the reproduction of animals (1651).

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[216] *ibidem,* 327-328 and 330-332.
[217] *ibidem,* 329-330.
[218] van den Berg (1965), *Het Menselijk Lichaam*, opposite page 40.
[219] Harris (1973), *The Heart*, 363-374 and 393-396.
[220] Pagel (1967), *Harvey's Biological Ideas*, 89-124; Pagel (1976), *New Light on William Harvey*, 37-41.
[221] Harveius (1628), *De Motu Cordis et Sanguinis*, 41-42.
[222] Pagel (1967), *Harvey's Biological Ideas*, 149-150.
[223] *ibidem,* 137-145 and 154-155. Servetus regarded the mixing of blood and air as a metaphor for divine inspiration (O'Malley (1953), *Michael Servetus*, 202-208).
[224] Pagel (1967), *Harvey's Biological Ideas*, 169-189 and 200-209.

Experimental medicine

Harvey was aware – as, incidentally, Galen was before him – that dynamic events such as the movement of blood could only be studied in live creatures. He therefore observed movements of the heart in a variety of live animals – reasoning that dynamic phenomena required an experimental approach. He concluded that the phase in which the heart becomes smaller and more solid, like muscles, as well as paler (*systole*), represents the active phase, in which the heart is emptied. The 'auricles' (upper chambers, now called 'atria', not yet regarded part of the heart) contract slightly earlier than the ventricles, mimicking a swallowing movement. Also the arteries expand when the heart contracts.[225] The liver does not move at all.[226]

A pump function of the heart does not necessarily lead to a theory of circulation, but Harvey had other arguments. A key issue is the quantity of blood leaving the heart. Calculating with weights rather than volumes, he estimated the output per half hour. Assuming 1000 heart beats (or a pulse rate of about 33 per minute) and an outflow per heartbeat between 1 dram (almost 4 grams) and an ounce (about 31 grams), the total weight of the ejected blood in this half hour would be between more than 10 British pounds (almost 4 kilograms) and more than 83 pounds (or about 31 kilograms).[227] It is impossible that the liver produces such quantities of blood.[228] Harvey also performed experiments with a tourniquet in animals: if the *vena cava* (hollow vein) is ligated below the heart, the part between the cord and the heart empties, while the heart becomes pale. Conversely, ligation of large arteries leaving the heart resulted in dilatation of not only the artery but also of the heart itself, while it became purple-coloured.[229]

Harvey also demonstrated that the flow in the superficial veins of the human arm is exclusively directed towards the heart (figure 13). For this argument he used the discovery

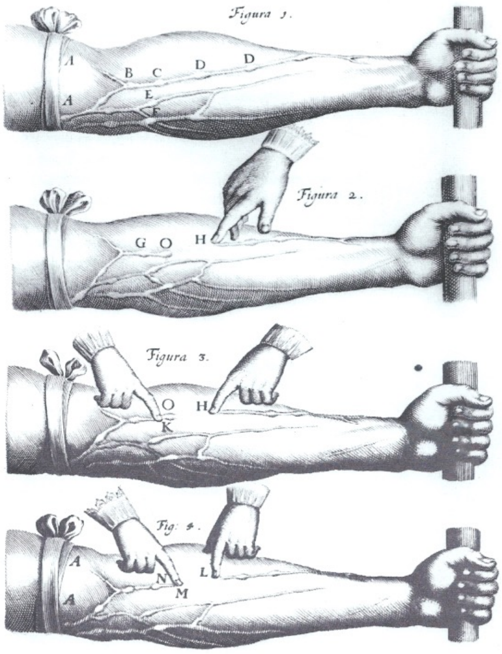

Figure 13*. Illustrations in Harvey's* 'De Motu Cordis et Sanguinis'*. The person depicted forcefully clenches his fist; a tourniquet (A) has been applied to the upper arm, sufficiently tightly to compress the local veins and to cause the veins between the tourniquet and the hand to distend, but not so much that the arteries of the upper arm are compressed as well.*

Top*: The sites where the veins are somewhat wider correspond with valves (BCDDEF).*

Second picture *from above: the examiner moves a finger from H beyond O, while exerting gentle pressure; this part of the vein remains empty, even if the finger returns to H.*

Third picture *from above: it is not possible for finger at K to squeeze blood beyond O in the direction of the hand.*

Bottom picture*: If the vein has been emptied from L to M, the vessel refills only by removing the finger at L, not by removing the finger at M.*

225 Harveius (1628), *De Motu Cordis et Sanguinis*, 22-30.
226 *ibidem,* 37.
227 Even the upper margin of Harvey's estimate is conservative. The average pulse rate at rest is about 72, the expelled volume per beat about 70 ml; this corresponds with more than 150 litre per half hour.
228 Harveius (1628), *De Motu Cordis et Sanguinis*, 44-45.
229 *ibidem,* 47-48.

of the valves in veins by Fabricius ab Aquapendente (1537-1619), his former professor of anatomy in Padua. Fabricius, who called these structures in veins 'little doors' (*osteoli*) rather than valves, had included an illustration with the same design as figure 13, but had not attributed any other function to them than preventing stagnation of blood in hands and feet.[230]

Harvey's conclusions

Harvey briefly encapsulated his findings in three theses:[231]

1. The heart receives blood from the hollow vein and pumps it without interruption into the arteries, in such large quantities that these cannot be the result of digestion by food.
2. Through the pulsations of arteries blood reaches all parts of the body, in quantities far exceeding what is required for nutrition.
3. The veins invariably return the blood to the heart; in this way the circulation is completed.

Harvey is undoubtedly one of the great men in the history of the natural sciences,[232] but despite his decisive experiments he cannot be regarded as a modern thinker, on a par with the all-out observationalist Galileo Galilei (1564-1642) or the mathematician Isaac Newton (1642-1727). Above all else Harvey was a system builder in the Aristotelian tradition, not a cool observer who patiently collected seemingly unrelated facts in a Baconian fashion. His own report of the discovery is telling:[233]

> I started to think whether [blood] might have some movement as if in a circle. Later I found that this was true, and that blood is driven and pushed from the heart via the arteries to the frame of the body and all its parts, by the pulse of the left ventricle of the heart, in the same way as [it is driven] to the lungs by the right [ventricle], through the arterial vein. [....] This movement can be called circular in the same manner in which Aristotle has likened air and rain with a circular movement of higher regions.[234]

Indeed Harvey interpreted his findings in a teleological fashion: the circulation of blood had an ultimate purpose, a truly Aristotelian *causa finalis*:

> Thus the heart deserves to be called the origin of life and the sun of the Microcosm, in the same way as, on another scale, the sun deserves to be called the Heart of the world. By its power and pulse blood is moved, perfected, invigorated and protected against decay and clotting. That faithful hearth fulfils it function by nourishing, warming and invigorating the entire body. But more about this elsewhere, when I will elaborate on the cause defined as purpose (*causa finalis*) of this movement.[235]

The reception of the circulation theory

The reactions to Harvey's *Exercitatio Anatomica* were not only mixed but were also complicated by several other issues, related or unrelated. To begin with, in discussions about the theory of circulation the subject often became contaminated with other, equally controversial matters in anatomy or physiology. The two most important of these were the

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[230] Fabricius ab Aquapendente (1603), *De Venarum Ostiolis*, 1.
[231] Harveius (1628), *De Motu Cordis et Sanguinis*, 43.
[232] Jardine (1999), *Ingenious Pursuits*, 110-114.
[233] Pagel (1976), *New Light on William Harvey*, 14-18.
[234] Harveius (1628), *De Motu Cordis et Sanguinis*, 41-42.
[235] *ibidem,* 42.

function of ‘lactic vessels’ (lymph vessels), which had also recently been discovered, and the lingering as well as nagging question whether or not the septum of the heart contained pores.[236] Also, several academics whose career had been built on teaching Galenic medicine felt that not only medical tradition but also their personal reputation was at stake. Finally the matter became mixed up with religious controversies, especially in the United Provinces, where factions of Protestantism struggled for power at newly established universities. The tone of the debates could be highly caustic, for example when adherents of Harvey’s theory were called *circulatores*,[237] which in Latin means ‘peddlers’ or ‘mountebanks’.

Telling the entire story requires a separate book, but the briefest of summaries might be as follows. Early adopters were especially found among members of the Royal College of Physicians of London and in the United provinces: Sylvius (Leiden), de Back (Rotterdam) and Walaeus (Leiden; after initial hesitations). Others were more gradually won over, for example Plemp (Louvain) and (Thomas) Bartholinus (Copenhagen). Inveterate adversaries were Primrose (Hull; an active pamphleteer), Riolan (Paris; the only one whom Harvey deigned worthy of a reply) and Parigiano (Venice).[238] Descartes deserves separate discussion.

René Descartes and the circulation of blood

René Descartes (1596-1650)

René Descartes was born in La Haye (Touraine); his youth was characterised by the absence of parents: his mother died during childbirth, when René was barely a year old, while his father, lawyer and landowner, was often away from home, mainly through his seat in the parliament of Brittany, in Rennes. Between the ages of 11 and 19 René was a boarder at the Jesuit school of La Flèche (160 km from home), where he was grounded in the scholastic version of Aristotelianism. He obtained a bachelor’s degree in law at Poitiers, but instead of the expected career in public office he enlisted in the French regiment of the army of the Dutch Prince Maurice, stationed in Breda. There he met Isaac Beeckman, who shared his interests in mathematics and natural sciences. A year later he went on a six-year tour of middle and southern Europe, leaving few traces. It was in this period that he developed the ambition to put natural philosophy on an entirely new footing. After a three-year stay in France without settling anywhere, Descartes lived from 1629 in the United Provinces almost without interruption, again at many different locations. He had started writing a book (‘Le Monde’) that should encompass and explain nearly all phenomena of nature, including mankind. It would never appear in this form; alarmed by the trial of Galilei in Rome, Descartes wished to avoid open conflicts with clerical or civil authorities. In 1637 he published three essays about optics, geometry and meteors, preceded by a general and partly autobiographical introduction, *Discours de la Méthode*; this also contained a section on the circulation of blood. In 1649 he was persuaded to move to Stockholm, as teacher in natural philosophy for the young queen Christina. He arrived in the autumn of that year and died in February of the next year from febrile disease, aged 54. His book on man (*L’Homme)* appeared only posthumously.

In 1638 the physician ***Henricus Regius*** (de Roy; 1590-1670),[239] who had studied in Leiden, Montpellier and Padua, was appointed professor of theoretical medicine and botany at the University of Utrecht, which had been founded two years before. Regius, impressed by the book *Discours de la Méthode,* arranged a meeting with its ***René Descartes*** (1596-1650; see box).[240] On his part, Descartes sought access to academic circles as he was seeking an audience for his new philosophy of nature; so the two men decided to collaborate.

[236] Maire, ed. (1647), *Recentiorum Disceptationes de Motu Cordis, Sanguinis et Chili in Animalibus.*
[237] Primirosius (1644), *Antidotum adversus Henrici Regii Venenatam Spongiam*, 30.
[238] French (1994), *William Harvey's Natural Philosophy*, 114-285.
[239] de Vrijer (1917), *Henricus Regius*.
[240] Clarke (2006), *Descartes*.

Descartes' accepted Harvey's idea of the circulation of blood, though he failed to acknowledge him by name, but did not share his conclusion that the systole constituted the active phase. Instead of Harvey's interpretation that the heart contracted and thereby became smaller during the systole, Descartes thought that a few drops of blood entering the ventricles of the heart became vaporous as a result of the heart's intrinsic heat (*feu sans lumière*, fire without light) and that the heart expanded as a result.[241] In terms of modern analogies, Harvey saw the heart as a pump, Descartes as an expansion engine.[242] It was this Cartesian version of the circulation theory that a student defended in the form of 11 theses at the University of Utrecht in June 1640, a text that had been carefully drafted by Regius and Descartes. It were these theses that prompted a pamphlet war with James Primrose and eventually ended with a ban of Cartesian philosophy at the Universities of Utrecht and Leiden,[243] but that is another story.

Descartes and the human body

The significance of René Descartes for the medical discipline as a whole can be easily underrated. True enough, in designing his model of the human 'machinery', also in other aspects than the movement of blood, he rather casually ignored many anatomical details that were already well known in his time. Also, his deductive method of reasoning led him to conclusions that proved untenable. But these shortcomings should not obscure the most important aspect of his work, viz. his basic tenet that all bodily processes, including many brain functions, can be explained on the basis of natural laws. In this way he provided an important impetus to the investigation of nature from a 'mechanical' point of view.[244] The human body may not be a clockwork, an example Descartes often used, but at least the analogy encouraged investigation of the 'mechanics of the body'.

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[241] Descartes (1664), *L'Homme*, 4.
[242] Lindeboom (1978), *Descartes and Medicine*, 72.
[243] French (1994), *William Harvey's Natural Philosophy*, 189-214.
[244] van Gijn (2005), 'Descartes en de Geneeskunde', 98.

Chapter 6

CAUSES OF APOPLEXY, 1625 – 1700

Apoplexy and the circulation of blood

Haemorrhage within brain tissue: the first clinico-anatomical report

The force of pulsating blood

Three types of apoplexy

Serous apoplexy

Confirmation from Oxford

Chemical explanations of apoplexy

No exit for ‘excrements’ of the brain

A synthesis in 1709

In chapter 4 I recounted how Niemann did not take Harvey's revolutionary theory into account or was even aware of it when he developed his explanation of apoplexy by assuming obstruction at the *torcular*, the point at the back of the head where the venous sinuses join each other. Later on, adversaries of the idea that blood went round and round in the body, of which there were quite a few, could of course feel free to embrace their own ideas about causes of apoplexy; they could adhere to either ancient opinion or to modern proposals, such as obstruction of blood at the *torcular,* where Niemann believed blood to be entering the brain instead of leaving it.

Apoplexy and the circulation of blood

Believers and non-believers

Someone who did not join the bandwagon of 'circulators' was no other than the influential physician ***Caspar Hofmann***. He had remained unconvinced by the theory of circulation, even after William Harvey had in 1636 paid a visit to Altdorf, where Hofmann was professor of medicine;[245] they had first met as students in Padua.[246] In general Hofmann retained ancient views, with some contemporary additions. In his *Institutiones Medicae*, published in 1645, he wrote the following brief comments about apoplexy:

> What is its cause? A single one, or several? I have always distinguished a single (proximal) one: obstruction. [....] With regard to the ventricles, something the majority of Physicians believes in, this falls to pieces as a mere phantasy if it is proved that they are not the production site of the spirits. Since this has been done before me by great men, [....], there is no need of others here. Perhaps only this. Before [the writings of] G. Nymannus had come into my hands, I regarded the channels of the brain,[247] as our Anatomists call them, as the site that was directly affected. Therefore, although I was first removed from him [in opinion], I now see eye to eye with him, and I totally embrace the *Torcular* he put forward. [....]
>
> With regard to the material, given the affected site in this case, it cannot be anything else than blood, while this is to blame by quantity rather than by quality. If there is anything wrong with it, it must be thickness, but it does not reach the thickness of phlegm or black bile.[248]

It is time to turn to explanations of apoplexy in which Harvey's idea about circulation is not merely acknowledged but actually used, in the sense that the movement of blood is no longer the passive result of many separate events, according to the needs and functions of each organ, but a primary, continuously active force, conveying its impetus to other structures in the body. In 1658, almost thirty years after Niemann's monograph, when the battles in medical circles about the revolutionary theory were still raging, another monograph on apoplexy appeared in Schaffhausen under the title 'Anatomical Observations from the Corpses of Persons taken away by Apoplexy, with a Discourse about its Site of Affection'.[249] The author of this book, which would be greatly appreciated by subsequent generations of physicians, was ***Johann Jakob Wepfer*** (1620-1695), city physician of Schaffhausen (see box on next page).[250]

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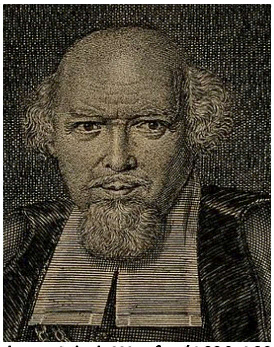
[245] Hirsch (1884-1888), *Biographisches Lexikon* volume III, 248.
[246] Wright (2012), *Circulation*, xv-xix.
[247] The *sinuses*? Hofmann's rejection of the ventricles as the site of apoplexy argue against the aqueduct.
[248] Hofmann (1645), *Institutionum medicarum libri sex*, 431-432.
[249] Wepfer (1658), *Observationes Anatomicae*.
[250] Eichenberger (1969), *Johann Jakob Wepfer*.



Johann Jakob Wepfer (1620-1695)

Wepfer was born in 1620, in Schaffhausen, Switzerland, as the eldest child of the judge Georg Michael Wepfer; his mother's maiden name was Stokar. After a sound education in his native town he studied medicine in Strasbourg and Basle, where he graduated in 1644. Wepfer spent the next three years in Italy. For two years he studied in Padua, where his tutors included the German Johannes Wesling (1598–1649) and the Dane Thomas Bartholinus (1616–1680).

On his return, Wepfer obtained his doctorate at the University of Basle in 1647 with a thesis on palpitations of the heart. Soon afterwards, he was appointed physician to the city of Schaffhausen. This office, probably shared with one or two others, involved providing care for the citizens, at home or in the local hospital, as well as for the convents in a larger area. Other tasks included advising the court of justice on medical matters, examining candidate surgeons, overseeing pharmacists and, importantly, performing autopsies. In 1650, he married Barbara Rink; they had eight children, five of whom survived to adulthood.

As Wepfer's reputation increased, he was consulted by the aristocracy of the independent counties in southwestern Germany. During his long life Wepfer accurately and succinctly recorded case histories, but he also wrote systematic treatises on a wide variety of medical subjects and animal experiments. Including correspondence with family members and colleagues, he left almost 12,000 handwritten pages. These were bought in 1774 by the University of Leiden for its library and still reside there. Wepfer is especially well known by neurologists on account of his two books on apoplexy (1658 and 1675). The only other book he published, apart from a disputation and dissertation as part of his studies, was on the use and abuse of hemlock (1679). A few decades after Wepfer's death a publisher in Amsterdam republished the two books on apoplexy with additions by other physicians (1724); several further compil-ations followed.

After a dedication to the Council of Senators of the Republic of Schaffhausen and a preface to the readership, Wepfer recounts, without further ado, four case histories of patients, with full clinical details up to the time of death, in each case followed by his personal observations at autopsy. Only then he presents his conclusions about the causes of apoplexy and explicitly relates them to the circulation of blood; meanwhile he compares his opinions with those of earlier authors.

The text of Wepfer's extensive treatise (over 300 octavo pages) is a continuous narrative, not ordered into chapters, in contrast with the sometimes overly sequestrated style of books in the middle of the 17th century. It often seems as if Wepfer is developing his arguments while he is writing. The only 'signposting' he provides is the use of larger type of print to highlight his main conclusions or findings. Nevertheless, it is possible to distinguish five main subjects in consecutive order, despite occasional overlaps.

Wepfer starts with a section in which he rides roughshod over the rear-guard of believers in the Galenic model of brain function and apoplexy; he then presents a detailed anatomical study of the arterial system of the brain. The last three parts are taken up by a discussion of three different types of apoplexy. In all three types he offers dynamic explanations and blood and blood vessels are the main factors; there is no longer a place in his thinking for phlegm or bile of whatever type. In dismissing these hypotheses he does not even take recourse to the sarcasm he reserves for other notions he regards as old-fashioned.[251]

Although Wepfer's clinico-pathological observations are the most important elements of his work, I have to deal first with his attempts to get rid of old-fashioned ideas.

Driving out the ghost of Galen

In chapter 4 I have pointed out that new ideas on brain function and apoplexy were by no means easily accepted by academic teachers and physicians. The traditional interpretations

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[251] Wepfer (1658), *Observationes Anatomicae*, 274-277.

of Galen's texts were still commonly adhered to; it is impossible to say whether indeed, as often happens, 'the mass outnumbered the elite in the democracy of thought'.[252]

Wepfer provides an indirect measure of the popularity of the old model by the forceful and often acerbic tone of the comments he provides in order to castigate timeworn assumptions. These were, in summary: firstly that there existed an intricate network of blood vessels, the *rete mirabile*, at the base of the brain but outside the hard membrane enveloping it; in this network the vital spirits from the heart were thought to be honed into animated spirits; secondly that the cerebral ventricles drew these animated spirits from the network and further perfected or at least stored them; and thirdly that it was via the ventricles that the animated spirits reached the nerves emerging from the base of the brain.

It is not necessary to pile Pelion upon Ossa and reproduce the multitude of arguments with which Wepfer demolished these positions;[253] they are largely consonant with the reasoning of Varolio and his followers, outlined in chapter 4. Wepfer was happy to find support for his criticisms in the writings of ***Caspar Hofmann***,[254] despite their disagreement about the circulation of blood. Wepfer directs the arrows of his censure especially at the person of ***Jean Riolan the younger*** (1577-1657), a highly influential professor of medicine in Paris and a staunch Galenist. Riolan published, apart from didactic texts,[255] a volume with criticisms of seven other anatomists and physicians;[256] among them were Bauhinus, Bartholinus and Hofmann. Wepfer's criticisms are often so personal that he seems unaware of Riolan's death, a year before his own book appeared in Schaffhausen. In the following passage Wepfer counters Riolan's argument against Hoffmann' opinion that the animated spirits travel to nerves via brain tissue and not via the ventricles:

> For he [Hoffmann] stumbled particularly over the issue how in fact the animated spirits, dissolved in the pool of the ventricles, can flow on into the nerves? A problem Riolanus thinks to have solved by questioning Hofmann how the animated spirits produced from the vital ones are diffused in the substance of the brain and subsequently flow into the nerves? But what if someone would question Riolanus about the manner in which the animated spirits are distributed through all the nerves - faster than the spoken word? The matter would be concluded. For it is certain that something can be dispersed in a moment from the brain to the nerves, whether spirits or any sort of ray, somehow related to rays from the sun. If passage is permitted through nerves [which are] denser than the brain, why not also through the brain? And what can impede its diffusion through the brain when nothing delays it in healthy nerves? If therefore nothing impedes their diffusion through the substance of the brain, why can't they be propagated from the brain to the nerves and to the entire body? After all, the nerves are continuations of the brain; together they even form a single organ.[257]

Although the discussion is rather speculative on both sides, one cannot help admiring Wepfer for the emphasis he puts on the lightning speed of the signals traveling through brain and nerves and the analogy in which he compares the animated spirits with sunrays. This notion can be regarded as a 'pre-idea', to borrow Fleck's term,[258] of the 'electrical' conduction of signals in the nervous system, in the same way as Galen's concept of vital spirits might be seen as a pre-idea of the oxygen carried by blood.

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[252] Fleck (1980 [1935]), *Entstehung einer Tatsache*, 164.
[253] Wepfer (1658), *Observationes Anatomicae*, 20-86, 44-47 and 141-144.
[254] Hofmann (1645), *Institutionum medicarum libri sex*, 146-150.
[255] Riolan (1626), *Anthropographia et Osteologia*.
[256] Riolan (1649), *Opuscula Anatomica nova*.
[257] Wepfer (1658), *Observationes Anatomicae*, 131.
[258] Fleck (1980 [1935]), *Entstehung einer Tatsache*, 35.

Haemorrhage within brain tissue: the first clinico-anatomical report

We now turn to one of the four case histories. To be true to Wepfer's style, I reproduce it in full, in order to render due justice to his astonishingly acute powers of observation; I will thereafter summarise the other three stories.

> ***Barbara Zuberin***, fairly close to seventy years of age, spent almost the entire course of her life as a servant; she had married in old age and somehow got through life. Widowed, she was admitted to the Hospital. She was of average build, and as far as I know she was not much stricken by disease, except that for some years her eyesight had begun to deteriorate; at some stage she was almost completely deprived of vision, yet she regained it to some extent, almost without medical assistance; then the malady further deteriorated. However, she never became totally blind. In either eye obvious early signs of grey cataract could be seen. For several months the people around her had already observed forewarnings of apoplexy, when her speech repeatedly halted; yet this defect of language soon disappeared. On January 10 of the year 1657, on a day of full moon, at three o'clock in the afternoon, while people thought she was healthy and spinning wool with her companions, she suddenly lost the use of speech and was seen to lean forward. She was soon taken to her bed by helpers; during that walk it was noticed that on the right side she still moved her foot, lifted her hand to her head and produced some words, though barely comprehensible. Suddenly, however, she lost all sensation and purposeful movement, with preservation of respiration (though soon afterwards this became laboured) and of the pulse; her face had a red colour. Few remedies were administered, because after the initial attack she was no longer able to swallow. On the same day, at six in the afternoon, she expired. On the following day in the afternoon I opened the head, together with Dr. HARDER, my most esteemed colleague, who is very learned in these matters. The roof of the skull having been removed, I cut away the middle part of the thick membrane in a circle, separated the falciform body from the *crista galli*,[259] and removed the lateral sinuses. Then, with the brain tilted to one side, I cut through all pairs of nerves, the carotid arteries near the *infundibulum*,[260] the *infundibulum* itself, the vertebral arteries where they appear at the back of the head, and finally the *medulla oblongata*, at its origin in the *foramen magnum*.[261] And so I took out the entire brain, freed everywhere from all its attachments, to allow me a more complete investigation of the immediate cause of this sudden event.
>
> From the isolated brain I removed the thick membrane that was still covering it: it appeared that the right half of the brain was entirely covered with blood, on its upper, posterior, inferior – but not as far as the base – and anterior surface, to the forehead. The brain was soft in these places and some kind of fluctuating fluid could be distinctly detected by palpation. During the removal [the fluid] had produced a tear on this side, from which a clot of pitch-black blood protruded, with the size of a nutmeg. Having inserted my finger, I gradually widened the tear with a small knife. I found a wide cavity, in front almost to the end, upwards almost to the falciform body and the third sinus;[262] at the back it extended to the midline, at a lower level even beyond it. The length of this cavity or abnormal hole exceeded eight inches, the breadth four, and the depth two-and-a-half inches.[263] It contained a blood clot resembling a hen's egg, apart from other smaller clots and fluid blood, in weight

[259] The *crista galli* is a small ridge at the inside of the skull base, in the middle of its frontal part (see figure 17 on page 86); at this ridge the falciform body (*falx;* see figure 11, page 55) is attached.

[260] The *infundibulum* is the bottom of the third ventricle, or Vesalius' 'funnel' (see figure 10, page 44).

[261] The *foramen magnum* (large opening) is the opening through which the spinal cord passes out of the skull.

[262] Now called the superior sagittal sinus (see figure 11, page 55).

[263] *'uncia'* ('nail's breadth') as a measure of length (inch): about 2,5 cm.

about eight ounces, or almost an entire pound.[264] At first we thought this was the lateral ventricle; but by searching more accurately we found that this cavity was not the ventricle, or some portion of it, but separate and abnormal, created by blood that had burst outside its vessels. [It originated] from some branch that had ruptured, a twig from a large branch of the anterior division of the carotid artery (figure 14).

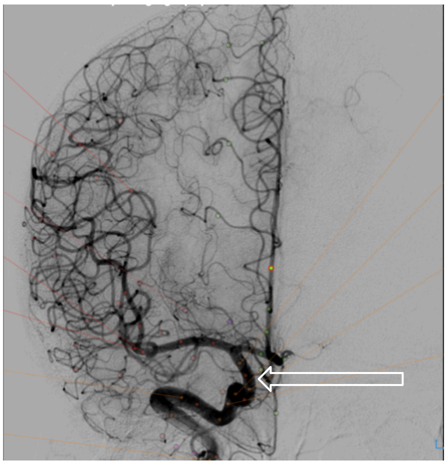

Figure 14. *Modern illustration to clarify Wepfer's decription of arteries. The reader looks at the forehead of a patient in whom the right internal carotid artery (ICA; arrow) has been injected with contrast agent; the blood vessels on the left side are almost invisible. After several curves the ICA divides into two branches, forming the shape of a 'T': to the side (the reader's left) the middle cerebral artery (large) and to the middle (the reader's right) the anterior cerebral artery (ACA; somewhat smaller).*

After this division the ACA crosses the optic nerve (not visible) and then curves upward at an almost right angle. In its course over the inner side of the right half of the brain the ACA gives off several smaller branches.

After this artery crosses the optic nerve, it proceeds with a considerable curve to the anterior and lateral part of the brain,[265] and is split in several branches not far from its origin, advancing between all the convolutions near the midline of the brain, and sometimes climbing to their surface, soon about to go down or to course further upwards over the convolutions of the midline, almost to the falciform body, divided into the tiniest twigs. Of those also quite a few clearly enter the substance of the brain, in more than one place. And that indeed one or more branches of this artery had ruptured in this place we could clearly and doubtlessly observe, for while we investigated its course on this side, we found that the primary branch and its ramifications, at the beginning as well as in the entire remaining course, was completely emptied of blood; all other arteries looked different, the posterior arteries on this side as well as some anterior arteries not originating from this branch. Furthermore, wherever this anterior lateral artery[266] and its branches went, blood clots met them, often tightly sticking to the arteries, and were as wide and high as these arteries diverge. [*The next paragraph is interpretative and follows separately below*]

In the entire space between the hard and the soft membrane there was no fluid anywhere, not even at the base or at the back. The right ventricle was intact everywhere; it contained blood-stained serum, but it would hardly fill half a walnut shell. In its posterior and lower part a small cyst[267] adhered to the choroid plexus. The left ventricle was completely empty; in the middle of the choroid plexus we found there a plaster-like, white, coarse and uneven stone, the size of a lupin bean; we saw smaller ones on either side in the plexus, the size of a millet grain or more, dispersed here and there. In the third ventricle we retrieved a blood clot the size of a bean. The pineal gland was not exactly at the beginning of the canal that opens from the third into the fourth ventricle; perhaps it was displaced a little upward, with the fourth sinus,[268] because of the size of its own swelling or that of the cerebral bleeding. In the beginning of this canal the walls were slightly tinged by blood-stained serum.

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[264] '*uncia*' as a unit of weight (ounce) is usually 1/12 of a pound.

[265] The term 'lateral' is a bit surprising, since the anterior cerebral artery courses near the midline; Wepfer probably refers to the inside of the right half of the brain.

[266] Again the term 'lateral' is puzzling.

[267] '*hydatis*', literally 'water-coloured gem'; these cysts are common and have no relation with disease; the same applies to the small calcifications described next.

[268] The *sinus rectus*, as it is called today (see figure 11, page 55).

> But the fourth ventricle was very clean, and we did not observe even the slightest defect in it. All four sinuses of the thick membrane were free of mucous bodies, nor did we see such bodies in another vessel of the brain. On the left side of the brain not even the slightest extravasation was present, nor was there any trace of clotted blood or other abnormality. In conclusion, this haemorrhage was sufficient to produce a most severe apoplexy. The internal carotid artery, entering on both sides of the pituitary gland, was on both sides covered by a bony and by a soft layer,[269] before as well as after passing through the thick membrane.[270]

A detailed and epochal report

Let me try to encapsulate the salient points of this detailed narrative. To begin with: the history is exemplary. First of all it contains some information about the patient's social background and previous diseases. The fact that Wepfer recorded the patients' name, though it may strike a modern reader as a lack of professional discretion, is in fact another manifestation of accurate recording that was far from common at the time. Also, and importantly, Wepfer has taken care to interview the people who knew her as well as those who were present. This produced the information that she had suffered episodes of halting speech, something that may be relevant in relation to apoplexy. In addition it emerged that the onset of the disease was instantaneous: she suddenly stopped speaking and leaned forward. And when she was assisted in getting to a couch, she could still move her right leg and arm – so not on the left side, which localises the problem in the right half of the brain.

In his examination of the brain Wepfer had ensured the help of an experienced colleague, which considerably enhances the status of his findings. The procedure itself was meticulous. It is worth noting that Wepfer used the dissection method of Varolio, in that he tilted the brain to one side after removal of the hard membrane and then cut it loose from all the arteries and nerves at the base of the skull on both sides, as well as from the spinal cord. When I recall the few post-mortem investigations that existed of patients who had died from apoplexy from 1550 onwards (chapter 4), these represent just a glimpse in comparison with Wepfer's careful dissection of the brain. The only exceptions are the two hydrocephalic children reported by Vesalius and Fabry. Let me list the main abnormalities in the brain of Barbara Zuberin.

1. There was a collection of blood clots in the right half of the brain, the largest of which had the size of a hen's egg; the cavity from which the clots were retrieved measured eight by four by two-and-a-half inches, with the largest dimension in the antero-posterior dimension. This cavity was separated from the right ventricle; with regard to the relative positions the cavity was presumably above the ventricle, since it extended as far as to the midline.
2. The clots were found adjacent to one or more secondary branches of the anterior cerebral artery, which normally supplies blood to a strip of brain tissue at the top, near the fissure that separates the two halves of the brain and in addition to the inner side of the hemisphere, where it faces the *falx* or falciform membrane (figure 11, page 55). The conclusion that these branches were actually torn is probably correct but perhaps conjectural, since tears in small vessels are often difficult to detect.

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[269] These coverings are normal.

[270] Wepfer (1658), *Observationes Anatomicae*, 5-11.

The force of pulsating blood

This conjecture brings me to the section I thus far omitted from the report:

> Therefore I recognised that by the continuous pressure of blood, after one or two of these arteries had ruptured, and blood had gushed into a deeper convolution, more and more space in the convolution was taken up, just as one wave is pushed forward by another. And while the deeper part of the convolutions was pressed down by the continuous pulse of the invading blood, the tissue elsewhere, being tender, delicate and soft, gave way to the impulse of the blood, was destroyed and easily expanded to this size, not unlike what happens in an aneurysm,[271] except that such a cavity is formed faster in the brain, because of its softness, than in any other part [of the body]. The outer surface of the convolutions remained intact, since the *pia mater* preserved it, by securing it and holding it together, so to speak. Also the bottom of this cavity was not ruptured, by the presence of the roof or rather fornix of the right ventricle, which is more like marrow and firmer than the tissue of the convolutions, which is more flaccid, forming the cerebral cortex, as Dr. Bartholinus calls it.[272]

Apparently Wepfer was carried away by the dynamism of the events that in his mind's eye should have taken place in producing the actual, static spectacle of ravaged brain tissue before his eyes. To such an extent, that he could not resist interrupting his style of accurate description by a vivid motion picture, as it were, of repeated gushes of blood spurting from ruptured arteries and displacing nervous tissue.

Three more clinico-anatomic observations

The story of Barbara Zuberin was in fact not the first but the second one Wepfer chronicled in his book. The reason for his order of presentation is unclear; at any rate it was not chronological, for her fatal illness occurred in January 1657, while the first patient in the book died in November 1655, the third in July 1655 and the fourth in February 1656.[273] So all four post mortem investigations took place within the limited a period of 18 months. This is quite remarkable, given the scarcity of autopsies in general, let alone of autopsies in patients who had died from apoplexy. It is therefore no wonder that Wepfer devoted a separate study to the subject, if he had not already decided on this before, since the preface is dated February 1658. I will briefly summarise the three remaining case histories; an account of Wepfer's interpretation will follow later.

Johann-Jakob Kenzingâ-Brisgojus (patient 1), approximately 45 years of age, a monk at the monastery of Freiburg, had landed there as an adolescent refugee from the ravages of the Thirty Years War in Northern Germany. Apart from chronic gout his health had been good; he preferred wine to solid food. On a November morning, having assisted the abbot at mass, he retired to his cell; a few hours later he was found on the floor, completely senseless; Wepfer was called, but despite interventions the patient died in the afternoon of

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271 The modern meaning of 'aneurysm' is a bulge formed in the wall of an artery; in the 17th and 18th century the term was often used for the combination of a firstly a small tear in an artery and secondly a collection of extravasated and clotted blood accumulated outside the vessel, in firm tissue such as muscle, thereby closing off the tear. A common variety of this occurred in coach drivers and other equestrians, at the back of the knee, where the artery could be damaged by the repeated friction with the upper rim of riding boots (Moore (2005), *The Knife Man*, 1-11).

272 Thomas Bartholinus (1616-1680) was a Danish physician and anatomist; he distinguished the soft and greyish outer layer of the brain ('like bark', in Latin *cortex*) from the whiter and denser medulla below; see Bartholinus (1651), *Anatomia*, 316.

273 Wepfer (1658), *Observationes Anatomicae*, 3-17.

the next day. At autopsy Wepfer detected no wounds on the skull, even after the scalp had been shaved. After incision of the hard membrane he found much sanguineous fluid around the brain, as well as a large collection of blood at the base of the brain and in all ventricles.

Anna Baltherin (patient 3), well over 60 years of age and mother of a few children, had worked in the local vineyards in her youth and adulthood and later functioned as midwife and wise woman. One evening in July she had gone out to collect lightwood but failed to return. The next day she was found dead near a hedge in the woods, with a superficial wound at the left temple. The local authorities asked Wepfer to perform a post mortem investigation, which he did in the presence of his younger brother Johann, also a physician.[274] It appeared that the wound had not even penetrated the skin. The brain looked normal on first inspection, but when it was taken out the base appeared covered with blood, mostly on the right side; the ventricles were filled with yellowish serum.

Jakob Reutinger Viterdinga (patient 4), some 50 years of age, had always been employed in the vineyards. Red blotches disfigured his face, which people attributed to excessive wine drinking. A few months before the current illness he had consulted Wepfer on account of excruciating chest pain; his treatment seemed successful at first, but when the pain returned the patient sought assistance from a hangman. A few weeks before his death he started to complain of vicious headache. Three weeks before he became blind; examination of his eyes showed no cataract or other abnormality. Afterwards he became bed-bound, often tossing around, eventually wetting his bed, while his feet became paralysed, the right side first. Four days before his death he was found 'apoplectic', in that he could not be aroused and did not speak or move. There is no mention of fever. At autopsy, when the hard membrane was cut, pale and corn-coloured serum flowed out with some force; the space between the hard and the tender membrane looked larger than normal. The surface of the brain and cerebellum was covered with a gelatinous substance, from which clear serum oozed when it was cut. The ventricles also contained an excess of serum. The substance of the brain was soft and flabby, almost like porridge, but not as fluid as in the case of Platter,[275] Wepfer wrote; he called it 'dropsy of the brain'. Despite repeated entreaties, Wepfer was not permitted by the patient's widow to open the chest or the abdomen – a detail that is not unimportant, as we shall see.

Before a discussion of Wepfer's ideas on account of his findings at these autopsies, I should point out that this last case history does not formally qualify for the diagnosis of apoplexy, even in Wepfer's own time. After all, the sudden onset, a vital criterion, is missing in this fourth patient. Wepfer writes that the patient 'was struck by a strong apoplexy', but in fact the onset of this stage of the disease was not witnessed and at any rate it represented a nearly terminal episode in the course of an illness that had been going on for several weeks. Still I should not therefore dismiss the report and replace it with a modern diagnosis,[276] since it has played an important part in the notions about apoplexy of Wepfer as well as of later generations of physicians. In fact a modern interpretation is possible thanks to the brilliance of Wepfer's description: instead of impressing his interpretation on his observations, he painstakingly collected the bare facts.

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274 Eichenberger (1969), *Johann Jakob Wepfer*, 12.

275 See page 53.

276 The time course of a few weeks, for the final episode at least, suggests an inflammatory process. To go one step ahead, the diagnosis of tuberculous meningitis is inescapable, as every neurologist will agree. Examination of the lungs might have shown similar lesions, related to the chest pain of a few months earlier.

Three types of apoplexy

At some point in his book Wepfer gradually shifts the subject matter, from criticisms of existing opinions to his own explanation of apoplexy. He distinguishes, two broad categories of apoplexy, as several 16th-century authors did: an impeded inflow of blood, carrying vital spirits, and an impeded outflow of animated spirits.[277] The former category takes place in blood vessels, the latter in brain tissue. But since he subsequently splits the latter category into two, I present Wepfer's model of apoplexy as consisting of three distinct types.

Destruction and compression of brain tissue by blood

Haemorrhage in the very substance of the brain, which Wepfer had found in the body of Barbara Zuberin, would in the course of time prove an important milestone in the history of neurology. In Wepfer's own time an important aspect was that his observation supported Varolio's still contested opinion that the animated spirits travelled to nerves via the tissues of the brain. Two of the other three patients dissected by Wepfer had also shown collections of extravasated blood, but at the base of the brain instead of within its substance.

It remained to be explained why all mental functions had been abolished, whereas the haemorrhage had affected only part of the brain. This was easier to understand if a haemorrhage occurs at the base of the brain, near the origin of nerves, as had happened in the patients described in the first and third case report. If the extravasation occurs in a more superior location, Wepfer reasoned, initially only local functions are disturbed; only as the blood clot further expands other blood vessels are compressed as well and apoplexy ensues. This sequence of events might explain that apoplexy can be preceded by a partial disturbance of mental functions, for example loss of speech or hemiplegia. And if the haemorrhage remains small, Wepfer proposes, it is reasonable to suppose that local effects remain the only symptom of disease and that the patient survives without apoplexy.[278]

Another important question is why arteries or arterioles burst. One category of causes, Wepfer proposes, in agreement with existing beliefs, is the condition of the blood. To begin with, its overall quantity may be excessive; among the examples he cites is Fabry's goldsmith (see page 58) and women who stop menstruating. Alternatively, the blood may be too thin, something he supposes to have been the case in the monk from Freiburg who loved his wine and was a frugal eater (case 1, Johann-Jakob Kenzingâ-Brisgojus). Apart from the properties of blood, a vessel might give way by lively heart action, as a result of physical exercise or mental agitation, or – a remnant of teleological reasoning – when the heart is beating forcefully in order to overcome an obstruction in an arteriole of the brain. Finally, Wepfer supposes the vessel wall might sometimes be damaged by corrosive fluids, or by smallpox, as he thought had occurred to a young girl in his practice.[279]

Apoplexy by a blocked inflow of blood?

This explanation of apoplexy is a return to the timeworn notion of obstruction, but now applied to blood vessels – that is, arteries, not venous structures, as Niemann had suggested. In discussing this possibility, first of all Wepfer argues, contrary to the opinion of

[277] Wepfer (1658), *Observationes Anatomicae*, 173.
[278] *ibidem,* 223-236.
[279] *ibidem,* 236-240.

some others, that the brain needs a continuous, uninterrupted supply of arterial blood instead of being supplied 'on demand'. He refers not only to authors who support his view but also to episodes of fainting (*leipothymia*). Most important, he points out the error in Galen's experimental finding that the functions of an animal would remain unharmed after ligation of both carotid arteries.[280] Wepfer explains that the vertebral arteries, situated deeper in the neck, still supply blood to the brain and refers to the arrangement of the arterial system, which he extensively described in his book.

Four interconnected arteries

In dismissing the 'wonderful net' to the realm of fairy tales Wepfer emphasizes that the internal carotid artery, once having originated in the neck from the common carotid artery, does not give off any branches before or during its passage through the skull base; he even provides an illustration, the only one in the entire book (figure 15).[281]

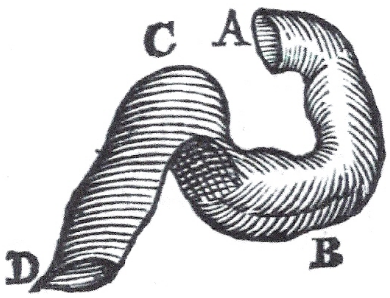

Figure 15. *The internal carotid artery as it courses through the skull base. At D it is still outside the skull base, at A it is about to perforate the hard membrane that envelops the brain. No branches pass out anywhere in this course.*

Wepfer then sets out to describe the course of the four arteries entering the skull, not only of the pair of carotid arteries in front, but also of the vertebral arteries at the back.[282] Wepfer largely confirms the configuration of the arterial system as illustrated in the second edition of *Syntagma Anatomicum*, a book by ***Johann Vesling*** (Weslingius; 1598-1649),[283] between 1633 and 1648 professor of anatomy and surgery (and later botany) in Padua.[284] An important finding was that there were communications between all these arteries, through which a kind of roundabout is formed at the base of the brain (figure 16, next page).

Any suggestion that this structure might correspond to Galen's 'miraculous network' should be resisted, because that fictitious structure (and the actual network in some animals) is situated outside the hard membrane that envelops the brain. Vesling's illustration is inconclusive about whether or not the anterior branches of the carotid arteries are connected, while he did not discuss the issue in his text. But Wepfer left no doubt:

> The remaining part of the foremost arterial branch at the base of the brain courses further forward, towards the crista galli. [*See figure 17, next page*] Where the brain is divided in two parts, the right branch is joined with the left one; in some I verified with an inserted probe that the branches were joined; however, soon afterwards they are again separated and, close together, both of them course separately to the crista galli, with which they are in close contact.[285]

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280 *ibidem,* 174-180.
281 *ibidem,* 38.
282 *ibidem,* 99-114.
283 Vesling (1647), *Syntagma anatomicum*, 195.
284 Ghosh (2014), 'Johann Vesling (1598-1649)'.
285 Wepfer (1658), *Observationes Anatomicae*, 109.

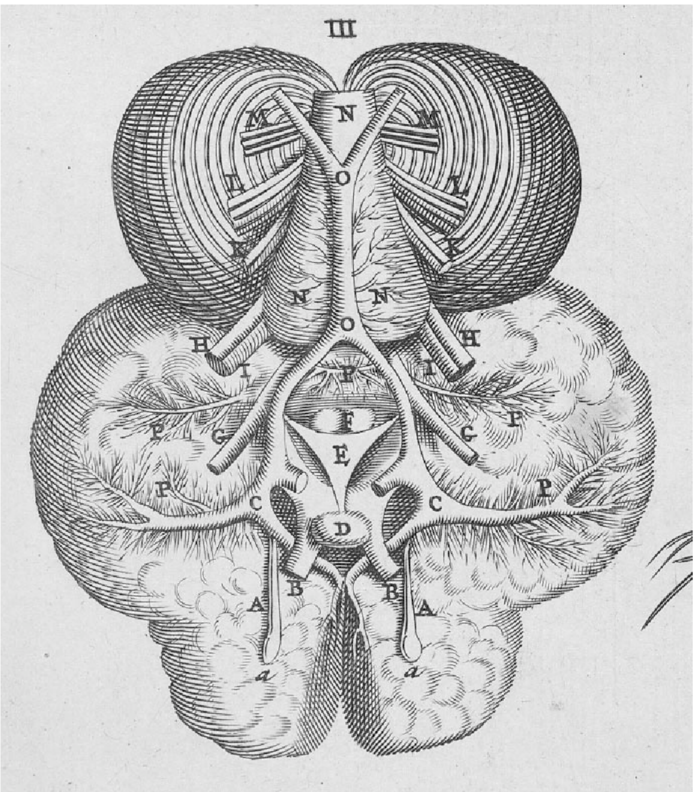

***Figure 16**. Srtructures at the base of the brain (Vesling 1647). The brain, cerebellum and brain stem are drawn rather symbolically, compared with those of Vesalius (figure 6, page 30) and of Varolio (figure 8, page 43); also the back is now at the top. Importantly, the arteries at the base of the brain are illustrated for the first time, though not quite accurately.*

The two vertebral arteries join into a single vessel O-O, split again into two vessels, which join the carotid system. In fact, these two vessels mainly serve the hind part of the brain (more or less like the fictitious system P-P-P, a half-hearted attempt to save Galen's miraculous network), while the connections with the carotid system on either side are, in reality, smaller twigs of these main branches.

The carotid arteries (cut off; stumps point at D) divide at C into a large middle branch and a small anterior branch. The anterior branches seem to touch each other in the midline (see figure 14, page 80) but are in fact connected.

Incidentally, the structure marked E is the infundibulum (Vesalius' 'funnel') in a purely symbolic form, while D is the pituitary gland.

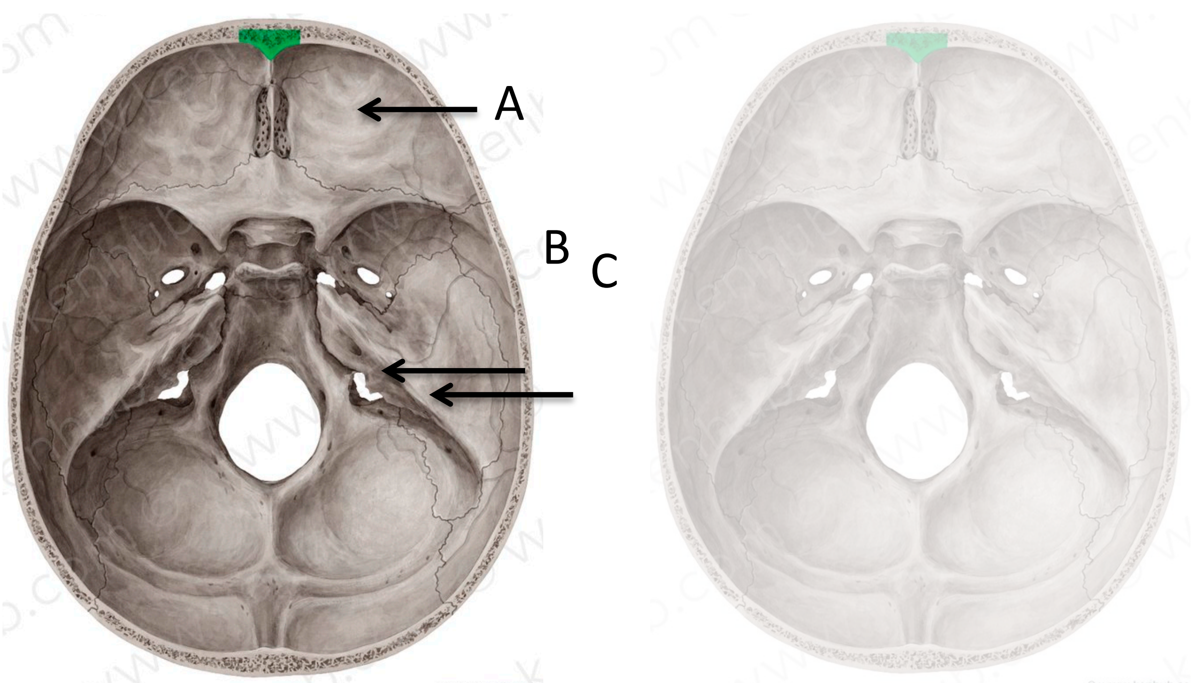

***Figure 17.** Modern illustration of the base of the skull, seen from the inside. A = crista galli (cockscomb), a ridge in the midline of the bony floor on which the frontal lobes rest. B = pituitary fossa (or Turkish saddle), normally containing the pituitary gland. C = the opening through which the carotid artery enters on either side (represented by a red bar on the left side of the right figure).*

With regard to the venous sinuses, where Niemann had located the origin of apoplexy, Wepfer concludes from his anatomical investigations that they act as receptacles of venous blood on its way back to the heart and that this venous blood is drained not only from the arteries of the hard membrane, but also from those to the brain.[286] Like Niemann, he had found whitish, gelatinous bodies in the sinuses of on dissecting the body of a 7-year-old boy, yet the patient had not suffered from apoplexy but from long illness of a bladder stone, leading to suppuration of the kidneys.[287] Actually, the very theory of circulation on its own already brings Wepfer to reject Niemann's explanation of apoplexy by obstruction of the sinuses at their point of confluence.[288]

Apoplexy by occlusion of arteries still possible?

Yet, despite the surplus of arteries to the brain and their mutual interconnections, Wepfer does not go as far as rejecting the possibility that their simultaneous occlusion can cause apoplexy. As an example, though one in which external forces caused the apoplectic state, he cites the miraculous history of the 22-year-old Anne Greene of Oxford. In 1650 she was accused or infanticide and sentenced to death by hanging (figure 18); after the execution her body was transported to a nearby building in order to be dissected later on. The physicians who first examined the body were Thomas Willis, who will appear later in my account, and William Petty; when, on opening the casket they discovered some faint sign of breathing, the two physicians applied all kinds of measures to revive her spirits. These attempts were eventually successful; in the end Ann Greene was pardoned and returned home. Wepfer recounts the story from a German translation.[289]

Figure 18. *The story of Anne Greene: the hanging (friends pull at her feet to shorten her suffering), the casket, and the bed she was put in; the other woman is at her side in order to warm her (Watkins, 1651).*

Wepfer cannot cite convincing examples of apoplexy by arterial obstruction from his own experience. Yet it is undeniable, also from his personal experience in dissections of patients who died from heart disease, that fibrous, friable bodies can be found in the

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[286] *ibidem,* 114-118.

[287] *ibidem,* 124-127.

[288] *ibidem,* 242-243.

[289] *ibidem,* 181-194. There are two British records of the story. One was a popular account published soon after the event; this was probably the source of the translation in German cited by Wepfer (Watkins (1651), *The miraculous deliverance of Anne Greene*).The other was an eyewitness account of William Petty, not published until much later (Landsdowne, ed. (1927), *The Petty Papers: Some Unpublished Writings of Sir William Petty*). It seems that Anne Green became a tourist attraction at the time.

ventricles of the heart, while it is not difficult to imagine that part of these bodies can break off and get stuck at the point entry of an artery in the skull base.[290]

Another possible manner of arterial obstruction, Wepfer hypothesizes, is within the smaller arterial branches of the brain, if mucous substances accumulate on their walls, a process that might be compared to the incrustations that can be found in the piping of water mills. If this occurs on one side, he reasons, the result is hemiplegia,[291]or loss of speech; but if it occurs on both sides together, true apoplexy strikes the patient. Particularly for this type of occlusion, of one or a few arterioles inside the brain, Wepfer regards therapeutic interventions eminently useful, especially venesection.

He cites several instances where the symptoms cleared after these measures, sometimes very rapidly, from his own practice as well as reports of colleagues.[292] The purpose of treatment is to displace the obstructive materials, as shown, Wepfer reasoned, by the example of a woman with apoplexy who began to improve as soon as her friends had started shaking her body and moving her around.[293] Venesection was supposed to have a similar effect, but Wepfer's reasoning to explain this effect is rather knotty, tinged by a remnant of the Aristotelian conception of goal-directed movement of blood. It is best to let him speak for himself:

> For first of all venesection counteracts the abnormal impulse of the blood, which often provides an opportunity for this obstruction. It rushes in smaller quantity to the brain, when, after blood has been drawn from the brachial vein for example, a sizeable portion makes for the arms in order to refill what was lost through venesection. Subsequently blood from the rest of the body and from the brain paces without delay to the heart, deprived as it is through that venesection, in order to bring help to the impoverished [organ]. The heart, liberated from the load that oppressed it before and during the paroxysm itself, propels the blood flowing back to it with greater alacrity, in a more proper order and in a quantity that will be wholesome for the brain. This [impulse] washes away what is causing obstruction and harm to the medullary substance and displaces it into the capillaries that are joined to the ends of the arterioles.[294]

A third cause of apoplexy: serum

So far for the first and second possible causes of apoplexy, in Wepfer's view: extravasation of blood with compression of brain tissue and nerves, or, alternatively, occlusion of several arteries at the same time. The third type was serous apoplexy, based on the case history of Jakob Reutinger. Though the diagnosis of apoplexy in this patient is highly questionable even without hindsight, Wepfer would, as I will show, later on buttress the notion of serous apoplexy with more convincing examples – in his own eyes at least. Eventually, the notion of 'serous apoplexy' would linger on until the 19th century before fading away, providing a perfect example of how blind alleys in the history of science can be forgotten if the present forms the point of departure.

[290] Wepfer (1658), *Observationes Anatomicae*, 195-205. Wepfer also cites, apart from his own observations, a dissection performed by Nicolaas Tulp of Amsterdam, which showed, according to the text and an accompanying engraving, a massive 'polyp' in the left ventricle, extending into both the aorta and the pulmonary vein (Tulpius (1641), *Observationum medicarum libri tres*, 54-58).Tulp attributed the death of the patient to apoplexy, since the amount of fluid in the brain was excessive, but Wepfer had his doubts.

[291] Wepfer (1658), *Observationes Anatomicae*, 205-209.

[292] One of these was again Nicolaas Tulp, case 7 (Tulpius (1641), *Observationum medicarum libri tres*, 14-15).

[293] Wepfer (1658), *Observationes Anatomicae*, 209-218.

[294] *ibidem,* 218-220.

Serous apoplexy

In order to explain the findings in Jakob Reutinger, in whom the 'apoplectic state' was part of a protracted illness, instead of a 'bolt from the blue', according to the usual definition, Wepfer once more resorted to a dynamic reconstruction of the course of events, as he had done in his explanation of the haemorrhage in brain tissue. But in this case he did not implicate whole blood, but a single constituent of it, viz. serum.[295]

> Quite a few things indicate that *Jakob Reutinger* suffered from an excess of serum, which became gradually collected in his skull: the lack of sleep, caused by the pain in his chest; it was made worse by the terrible headache, then his blindness[296] developed. The accumulated [serum], flowing further down through the foramen in the back of the head next to the spinal cord, brought about the involuntary loss of urine, then the paralysis of the feet, and finally a sudden and very severe apoplexy. And what fully persuaded me that serum had brought about apoplexy not only by filling all ventricles and the space between the membranes and the spinal opening through which the spinal cord goes down but also by compressing the brain and the cerebellum, was that the space between both membranes was wider than it normally is.[297]

For the notion of 'serum overload' Wepfer finds support in the writings of Carolus Piso (see pages 59-60). He praises him for drawing attention to the role of an excess of serum as a cause of apoplexy and exculpates him for his mistaken opinion about its location (the ventricles of the brain), because at the time of his writing Harvey's theory of the circulation of blood was not yet known.[298] Wepfer reasons as follows:

> Serum [....] is an inseparable companion of blood and because they are transported together through the entire brain within the capillary arteries, and [because] it is fine and almost free of viscosity, so that it can pass the smallest openings and make its way into the narrowest channels, in the same way as water gets into the little cavities of sponges, or into substances that are tighter than sponges. In addition it is not difficult to separate it from blood, as is testified not only by urine, tears and sweat, but also by certain diseases, as proved by catarrh, serous diarrhoea, arthritis and other ones. The golden book of Carolus Piso, *De Serosa Colluvie,* which should be consulted, provides clear examples of this matter in several afflictions, described from head to toe; it will teach the attentive reader that perfectly pure serum, often suddenly partitioned off from blood, emerges as the cause of many illnesses.[299]

Wepfer explains the separation of serum from the rest of the blood by the same pulsatile force that can cause haemorrhage into the brain. But in this case, he hypothesizes, it is not whole blood but only serum that is forced through tiny openings in the terminal ramifications. The subsequent obstruction of animated spirits takes place by a blockade of the minute openings in nerve tissue into spirits enter to reach the nerves. It was a common notion at the time, at least for those who no longer believed in transport of spirits via ventricular fluid, that brain tissue and nerves contained tiny,

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[295] I have noted before that it was well known that blood, if collected in a receptacle after venesection and left standing, showed sedimentation of heavier particles to the bottom, leaving a clear layer, serum, above it.

[296] Wepfer uses the expression '*gutta serena*', or 'clear cataract', to indicate that the blindness could not be explained by discernible abnormalities in the eye.

[297] Wepfer (1658), *Observationes Anatomicae*, 290-291.

[298] *ibidem,* 271.

[299] *ibidem,* 246-248.

invisible channels; otherwise spirits could never travel to their precise points of destination.[300] It was an hypothesis as inescapable as Harvey's supposition that there should exist minute blood vessels that connected the arterial and the venous system:

> The first thing that must be mentioned before everything else with regard to the obstruction, is that the brain and the cerebellum are porous, not only because of the relationship with arteries, of which [both] receive very many – pores of this type are visible in great number – but also because of the animated spirits that have to be transported into nerves on either side. That these spirits must consist of some kind of material is clear from almost any separate paralysis of a body part and from ligatures of nerves, for if these spirits had to be classified as a category of spiritual qualities, they might easily overcome these obstacles (in the same way as light goes through the thickest window panes and smells of bait are perceived by fishes swimming in the deepest pools).[301]

Obstruction of nervous pathways by serum is not an all-or-nothing-phenomenon, according to Wepfer; patients may suffer hemiplegia or other partial defects and subsequently recover or at least survive. Other patients in his practice experienced premonitory symptoms or even repeated episodes over time before ending up with a true apoplexy. In one patient, who went through an episode of not being able to read what he had written himself, Wepfer again described the symptoms in such admirable detail that a modern neurologist can exactly localise the site of the lesion.[302] Of course Wepfer had no proof to distinguish serum in these episodes from other possible causes of obstruction, but he based his conclusions on circumstantial evidence.[303]

A 'postscript' in 1675

Seventeen years after the publication of his monograph, when Wepfer's fame had spread widely across the German-speaking regions of Europe, he had the book reprinted – at the request of his friends, he wrote in the introduction. In addition, he added reports of seventeen new cases of apoplexy, seven of which were accounts he had obtained from colleagues.[304] After each of these case reports Wepfer wrote a section with commentary (*scholia*), often extensive, especially if autopsy had been performed and the brain could be examined (nine patients). Three of these nine patients had died after severe head injury, three others after a long-standing illness; needless to say, all had passed through a stage of 'apoplectic' unresponsiveness, but the findings at post mortem do not help to confirm or to supplement any of Wepfer's previous observations and conclusions about the causes of apoplexy. One other patient was found unconscious by his servants and had still breathed for some time according to their testimony, but on dissection his chest proved to be filled with blood. The case histories of the two remaining patients, both from his own practice, deserve to be summarised.

Ursula Alberlin (case XIV)*,* an unmarried girl of 23, employed as servant at a village inn, twice felt something snap in her head while she was carrying a heavy load of cattle food, in the summer of 1667. From that time she had some difficulty containing her urine, but otherwise she lived on as before. In December of that same year she sought shelter against the cold in a church; once inside, she suddenly lost all sensation and motion in the left arm

[300] Smith (2007), 'Brain, Mind and Medicine', 17-18.
[301] Wepfer (1658), *Observationes Anatomicae*, 244.
[302] van Gijn (2015), 'A Patient With Word Blindness in the Seventeenth Century'.
[303] Wepfer (1658), *Observationes Anatomicae*, 263-270.
[304] Wepfer (1675), *Observationes Anatomicae, cum Auctuario*.

and leg, within a few minutes; also her mouth was awry and she spoke with difficulty. She was taken home, stayed in bed for two weeks, was sometimes delirious and complained of headache. When Wepfer saw her, eight weeks after the event, the paralysis of the arm and leg was unchanged; she spoke normally and had a good colour. The countess of the region supplied the drugs Wepfer prescribed. The patient learned to walk again with a stick, but in the following summer (of 1668) the weakness of the left side worsened; the headache returned and became steadily worse. In January of the next year she suffered from catarrh of the chest; she coughed not only phlegm but also blood clots. Her abdomen and left arm became swollen, she developed gangrene of the right foot and she died in March 1669.

Through persistent entreaties Wepfer was permitted to perform a dissection. On opening the hard membrane of the brain, yellowish serum flowed out; a gelatinous, transparent, yellowish membrane covered the entire surface of the brain. The right half of the brain, near the ventricle, contained two abscesses, about the size of a hen's egg; one of these was inadvertently cut. The chest was not opened, because Wepfer was called away.[305]

Ursula Pulen Frisen (case XV), 37 years old, from a moderately wealthy family of farmers, had several children and was again four months pregnant. For a long time she had complained of headache and dizziness, when, one morning in May 1661, crouching because of violent headache, she suddenly lost her voice, fell down like a log and was deprived of all sensation and motion, except breathing. Transferred to her bed, she was motionless for three days. Subsequently it became clear that she could move her left arm and leg; within a month, she was able to walk when supported, dragging her right foot and with a useless right arm. In October she was confined of a healthy baby; she showed no concern for this infant or the older ones, was often 'delirious' or afraid of harmless noises, and on several occasions had to be stopped from attempts to hang or otherwise harm herself. Gradually she became quieter, but she lost weight and became pale in the face. She became pregnant once more and bore another child, which she breast-fed until her death. On February 21, 1664, she was woken up by a severe pain in the right chest, which even increased over the next few days. Coughing frequently caused her much trouble; the sputum was blood-tinged. She died on February 26.

Wepfer, though he does not mention any personal involvement in her treatment, was permitted to perform a dissection, owing to the intervention of the abbot from a nearby monastery. In the head, the hard membrane was swollen and tense, as if inflated by vapours; its vessels were full of blood. The soft membrane seemed to squeeze and flatten the convolutions. The surface of the brain seemed swollen on both sides; everywhere copious serum flowed out when it was damaged. Both ventricles contained blood-tinged serum; the same fluid was found at the base of the brain. The walls of the ventricles "looked orange-yellow, as if covered by rust; for it was lined with yellow slime, similar to what is seen around iron-containing waters and often incrusts the surface of stones and the soil." The right lung was firmly attached to the pleura; when this had been torn loose, up to two pounds of pale serum appeared in the posterior cavity of the chest. The lobes of the right lung were all large, hard, tense and red, or rather spotted with red, their outer membranes solid and thickened. On incision, both lungs were full of blood-tinged grime, watery, foamy and in the deeper parts purulent.[306]

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[305] *ibidem,* 392-400.
[306] *ibidem,* 410-416.

In his comments about the girl of 23 years, Wepfer attributed the two abscesses (or tumours – he used both terms) to the episode in which she had to carry a heavy load; the two snaps she had heard corresponded with the two tumours, in his view. This is but one example of the precision with which Wepfer tried to fit all the recorded observations into his conceptual framework of the anatomy and physiology of the body. His reasoning is long-winded, circuitous and often incorrect in the opinion of modern physicians. Yet the most important and perhaps the unique aspect of his writings is that he did not allow his interpretations to encroach upon his observations: he patiently collected the facts as they were, from the history, from the examination and from the findings on dissection. It was not until then that he patiently and painstakingly tried to fit the pieces of the puzzle together into a meaningful whole. To continue Wepfer's reconstruction of the course of events in the servant girl: he attributed the left-sided hemiplegia that occurred six months later mainly to an excess or serum, perhaps with some contribution from the two 'tumours' (he was well aware that body parts often corresponded with areas of the brain on the opposite side). Also, he blamed dietary factors for the recurrence of the headaches that had initially accompanied the hemiplegia, and attributed the dizziness to the two tumours, after an extensive detour into his experience with brain cysts in mules. With regard to the cause of death he mentioned the gangrene of the right leg but remained somewhat evasive – after all he had not examined the lungs and the heart.[307]

For the sad story of the disease the farmer's wife went through in the course of three years Wepfer's reconstruction is as follows: the swollen blood vessels of the hard membrane had caused the headache,[308] the headache in turn caused a temporary surge of serum that caused the apoplexy by entering into the deep regions of the brain, but could not be retrieved in full quantity at the time of autopsy, three years later. Her death was caused by the inflammation of the lungs and their membranes ('pleuritis').[309]

Reinterpretation of the facts

So, with these two case histories Wepfer added more weight to the notion of serum as a cause of apoplexy. Almost unavoidably, the interpretation of a modern neurologist will be different. There is no doubt that all aspects of the disease of the servant girl, of the brain as well as the lungs, are readily explained by chronic inflammation; fever is not mentioned in the report and would certainly have been recognised, so the cause was almost certainly tuberculosis, as in Wepfer's first case of 'serous apoplexy' (page 83). In addition, the farmer's wife died from an afebrile pulmonary infection, for which tuberculosis is the prime candidate. The history of progressive headache and the abnormalities in her brain are equally consistent with tuberculous infection. Pathologists from the early 19th century saw similar 'membranous' layers covering the surface of the brain, which they could illustrate by means of lithography.[310] Involvement of major brain arteries in tuberculosis is no longer well-known in Europe but common in developing countries.[311] It cannot be emphasized enough that these modern interpretations are made possible by Wepfer's meticulous reporting, in which he carefully avoided contamination of the facts by his subsequent interpretation.

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[307] *ibidem,* 400-410.

[308] It was well known at the time that the membranes of the brain were pain-sensitive, unlike brain tissue.

[309] Wepfer (1675), *Observationes Anatomicae, cum Auctuario*, 410-416.

[310] Cruveilhier (1829-1835), *Anatomie Pathologique*, livraison VI, planche 1; Bright (1827), *Reports of Medical Cases*, volume 1, plate 29.

[311] Wasay, et al. (2018), 'Cerebral Infarctions'; Kalita, et al. (2018), 'Arterial system in tuberculous meningitis'.

Wepfer's legacy

A summary of Wepfer's findings is appropriate, since he not only spent much energy in convincing his readers that Galen's ideas about apoplexy were obsolete, but also made important and novel contributions himself. First, by adopting Varolio's method of removing the brain from the skull in his dissections,[312] he studied the anatomy of the arterial system. Moreover, he did not limit his inspection to the surface and especially the base of the brain, as Vesling had to some extent done before him, but he followed its ramifications to its deepest parts.

Secondly, he distinguished three kinds of apoplexy; each of these was a dynamic event, related to Harvey's theory of the circulation of blood. The common factor was preventing spirits to reach the nerves.

a) by simultaneous occlusion of all arteries of the brain, before or after ramification of the four main arteries; Wepfer had no examples to prove this variant, but he thought it a definite possibility;
b) by rupture of a blood vessel, at the base of the brain or in the very substance of the brain; this last subtype type of apoplexy was completely novel;
c) by an excess of serum, invading brain tissue; this type of apoplexy has no counterpart in the modern notions of stroke and has therefore been ignored by historians of medicine;[313] nevertheless it played a large role in thoughts of Wepfer and those of later generations.

Thirdly and most importantly, Wepfer had an exemplary style of reporting. To begin with, he listed extensive details of the clinical history, for which he must have interviewed bystanders, relatives and neighbours. In his description of the symptoms he used common language – as far as this is possible in Latin – instead of transposing them into medical terms. Wepfer applied the same punctiliousness to his account of dissections, the more so since he could not rely on illustrations, apart from a single section of an artery. It is this twin inventory of details, one collected during the illness, the other after death, that makes up the core of medical knowledge for the centuries to come, the 'clinico-pathological correlation'. In trying to reconstruct the course of events, Wepfer joined the pieces of the puzzle together according to the state of knowledge in his time – and a neurologist in 2019 can combine these same carefully collected details according to the state of knowledge some 350 years later. But the facts have not changed.

Wepfer was well aware that he was living in a world where understanding of nature was incomplete and that many more facts needed to be collected. In his dedication of the 1675 collections of new cases, to an important councillor and diplomat in the Republic of Schaffhausen, Wepfer acclaimed the foundation of scientific societies dedicated to experiments in many regions: first of all in England, but also in Germany (*Collegium Naturae Curiosorum*), Italy (*Academia dei Lyncei*), with plans for similar institutions in Denmark, France and Rome.[314]

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[312] Wepfer (1658), *Observationes Anatomicae*, 14 and 23.

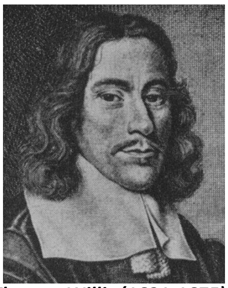
[313] Examples are Mani (1982), 'Wepfer's work on apoplexy', 49-51; and Storey and Pols (2010), 'History of cerebrovascular disease', 404-405.

[314] Wepfer (1675), *Observationes Anatomicae, cum Auctuario*, 309-310.

Confirmation from Oxford

Wepfer's work was extensively cited in the chapter on apoplexy of a book on the 'soul of non-thinking creatures' (*anima brutorum*) that appeared in 1672, three years before the demise of the Schaffhausen physician. Its subtitle was 'which in man is the vital and sensitive [soul]'. So the term 'soul' (*anima*) should not be understood in a moral or religious sense, but as the vital principle that keeps the machinery of the body going.

Its author was ***Thomas Willis*** 1621-1675; see box).[315] He agrees with Wepfer that apoplexy is caused, in general terms, by obstruction of either inflow of blood and spirits to the brain or outflow of spirits to the nerves.[316] With regard to obstruction of arteries to the brain, Willis had already drawn attention to the interconnections between the main cerebral arteries in an earlier book, on the anatomy of the brain, published in 1664. Wepfer had correctly described them but merely hinted at their signifycance as 'emergency passages'. Willis provided an accurate illustration and so improved on Vesler's plate, thanks to the skilful engraving of Christopher Wren (figure 16, next page). In addition, he was more explicit than Wepfer:



Thomas Willis (1621-1675)

Willis was born in Wiltshire, as the first child of a farmer and steward; he was named after his father. Two more boys and several girls would follow. Around 1630 the family moved to a village near Oxford; his mother, Rachel Howell, had inherited a small estate there, but she died soon afterwards. Thomas junior received a solid classical education at a private school in Oxford; at the age of 16 he matriculated at the university, while serving as a houseboy for the canon of his college, in return for his lodgings. After he graduated Master of Arts in 1642, the Civil War broke out and an epidemic fever snatched away his father and stepmother; Willis became responsible for two farms as well as for his siblings and stepbrothers. After two years in the Royalist army, which was eventually defeated in 1646, Willis returned to the university. At the end of that same year he graduated bachelor in medicine with license to practise, after merely a few months of training.

He then started his medical practice from scratch, by touring the markets of neighbouring villages. Meanwhile he had time to read and became aware that his medical knowledge was insufficient. He felt inspired by the chemical writings of the Flemish physician Joan Batista van Helmont (1579-1644). Despite some shyness and a stammer, Willis became involved with an informal group of academics dedicated to 'experimental philosophy', including the flamboyant physician William Petty (1623-1687) and the young Christopher Wren (1632-1723); later members were Robert Hooke (1635-1703), Richard Lower (1631-1691) and Robert Boyle (1627-1691). When his practice had sufficiently grown, Willis married Mary Fell in 1655. After the restoration of the monarchy in 1660 he was nominated Doctor of Medicine as well as professor of Natural Philosophy at Oxford University and he became one of the founding members of the Royal Society. With Richard Lower he performed dissections of the brains of humans and of several animal species; he published extensively. After the great fire of London (1666) he moved to the capital and became a famous physician; his practice no longer allowed him to participate in scientific activities. He died at the age of 54 and was buried in Westminster cathedral.

> These vessels have many possibilities to connect with each other; of course in order to ensure that with blood on its way to the different regions of the brain there is more than one pathway open for each [of the vessels]; this is safer. For if one or the other access is closed off, another one is easily found in its place. If, for example, the carotid system is obstructed on one side, the vessels on the other side supply both territories. Even if both carotids are crammed, their duties are taken over by the vertebral [arteries]; vice versa, the carotids make up for deficits of occluded vertebral arteries. In this manner the extraordinary construction acts as a safety measure to ensure that there is no shortfall in the blood supply anywhere, in whatever

[315] Dewhurst (1981), *Willis's Oxford Casebook*, 1-59.
[316] Willis (1672), *De Anima Brutorum*, 264.

> part of the brain or its appendages within the skull. If it has happened by chance that three of them are occluded, it will be through only a single [artery] that the provided [quantity of] blood immediately supplies all channels and twigs of all other [arteries], given there are four separate entries for this fluid, at some distance from each other.[317]

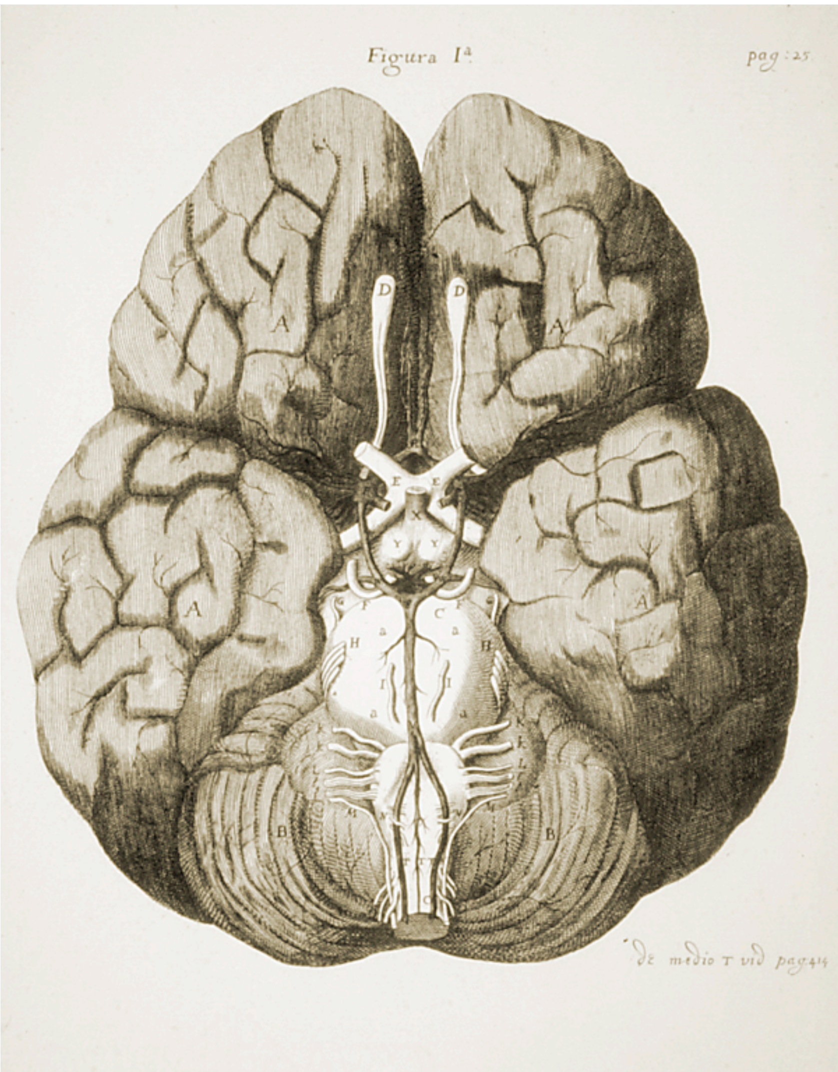


Figure 19. *View of the base of the brain, from Willis's 1664* Cerebri Anatome. *Engraving by Christopher Wren (1632-1723), the later architect of St. Paul's cathedral in London. The two vertebral arteries (bottom of figure; dark) first join and then separate again. On each side the main branch (represented here as being rather narrow) goes sideways to the hind part of the brain. The other branch goes on to connect with the carotid artery (cut off), next to the crossing of the optic nerves. The carotid artery divides into a large branch going sideways between the two lobes of the brain, again dividing in its course, and an anterior branch, which crosses above the optic nerve and connects with the other anterior branch. Thus the arteries form a circle, now named after Willis. Incidentally, 'X' indicates the infundibulum.*

But Willis went further than drawing attention to the probability that the blood supply of the brain would be preserved via these byways if one or more of the four main arteries had become occluded:

> I have proved this by experiment, quite often performed with the greatest pleasure; admiration has not been lacking. Indeed, as often as I injected fluid that was mixed with ink into one or the other carotid artery, the ramifications on either side were immediately stained with the same colour - even the main branches of the vertebral arteries. What is more, if such an injection through a single [vessel of] entry was repeated at different times, the vessels running to whatever nook and corner of the brain and cerebellum were stained with the same colour.[318]

So Willis applied the novelty of a medical experiment, injection of ink-coloured fluid in the brain vessels of a cadaver, in keeping with the tradition that had developed in the

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317 Willis (1664), *Cerebri anatome*, 93-94.

318 *ibidem,* 94.

circle of his friends in Oxford. Later, after the restoration of the monarchy, this circle would be transformed to the Royal Society, based in London. Willis interpreted the results as proof of the hypothesis he formulated on the basis of his (and Wepfer's) accurate observations of the anatomy of the arterial system. Another argument for the interconnections between the major arteries of the brain was the chance finding of an occluded carotid artery when he dissected a patient who had died from a disease of the internal organs, unrelated to the brain:

> Not so long ago I dissected the corpse of a deceased person who had succumbed to a giant tumour of the bowels, which had eventually ulcerated. When I had opened his skull and reviewed the brain and its connections, I found that the right carotid artery, as it entered the skull, was plainly bone-like or rather stone-like, while its cavity was almost entirely occluded. Because the inflow of blood along this route was closed off, I therefore wondered why the patient had not previously died from Apoplexy. However, this was not at all the case, since he had full command over his mind and intellectual function up to the last moments of his life. Indeed nature had made provisions for a quite useful remedy against that danger of Apoplexy.[319]

So the experiment 'in vitro', by means of injection of black ink, was supplemented by an experiment of nature, 'in vivo'. Like Wepfer, Willis had never performed a dissection of a patient who actually did suffer from apoplexy after the arteries of the brain had become occluded. But while Wepfer did not wish to exclude this possibility, Willis emphasized the improbability of such an event.[320]

The observation of a calcified (?) occlusion of the internal carotid artery at its point of entry in the skull is intriguing in view of theories about arterial disease that would emerge more than two centuries later, but this isolated fact had no consequences at all for medical thinking at the time.

Apoplexy by lesions of brain tissue: Willis extends Wepfer's observations

In fact Willis had no experience at all with dissection of the brain in patients with spontaneous apoplexy of any category, to his own disappointment.[321] In his chapter on apoplexy in *On the Soul of Brutes* he therefore had to rely on his own anatomical findings and on Wepfer's observations, in which, Willis wrote, nothing should be altered, apart from a few additions.[322] Almost as a matter of course he agreed with his modern colleagues that animated spirits were produced from blood in the substance of the brain, through a process similar to distillation. A peculiarity in Willis's model of brain function was that he attributed the conscious perceptions and actions to the brain (cerebrum), but 'automatic' functions such as respiration and hart movement to the cerebellum.[323] He even went as far as supposing that attacks with sudden cessation of heart action and respiration might result from an apoplexy of the cerebellum;[324] I must abstain from pursuing this subject any further since we are primarily dealing with apoplexy of the brain *sensu strictu*. Also interesting, yet again outside the scope of the

[319] *ibidem,* 95.
[320] Willis (1672), *De Anima Brutorum*, 265.
[321] *ibidem,* 275-276.
[322] *ibidem,* 265.
[323] *ibidem,* 263.
[324] *ibidem,* 266-267.

current thesis are the different regions of the *cerebrum* to which Willis assigned intellectual functions or the integration of sensations or movements.

With regard to structural lesions of the brain as causes of apoplexy, Willis agreed with Wepfer's two categories (ruptured blood vessels and a surge of serum) but he adds a third and relatively rare cause, though without supporting observations: rupture of an abscess.[325] The apoplexy may manifest itself only once, as an unexpected and catastrophic event, Willis writes, but it can also have a stuttering course. In those cases, he proposes, the obstructive material causes transitory symptoms, because they percolate throughout the brain, first obstructing pores (or inactivating spirits) in its peripheral parts, later in more central and more vital areas.[326]

Chemical explanations of apoplexy

In the course of the 17th century scientists increasingly recognised and used chemical definitions of matter, also in the explanation of disease. With regard to apoplexy, new ideas about causation mostly revolved around changes of blood by means of chemical factors, causing obstruction of blood flow. I will briefly sketch the developments within medicine as a whole, before returning to the subject of apoplexy.

Philippus Aureolus Theophrastus Bombastus von Hohenheim (1493-1541)***,*** who adopted the name ***Paracelsus***, had been an early pioneer among physicians in his – highly unsystematic – attempts to put medicine, and natural philosophy in general, on a completely new footing, based on chemistry instead of on ancient writings.[327] His train of thoughts is not easy to follow, but at least his view on apoplexy can serve as an example; also it adds to the panorama of opinions 16th-century physicians fostered about this disease:

> *Gutta (*paralysis, *apoplexia*) is any body part that loses its own power, such as [with] gonorrhoea, similarly with a defect of speech, or sight, or hearing.[328] And the disease is nothing else than that a body part can no longer perform its *officium.* There is no defect in the stomach or in nutriments. It also involves paralysis in the heart and the spleen. The cause is that *synovia* is separated from its body part; for there is no body part or it has *synovia*, like in joints.[329]

In the 17th century the Flemish physician ***Joan Batista van Helmont***, who worked in isolation because he had been put under house arrest by the Spanish inquisition,[330] extended his approach; for example, instead of Paracelsus's salt, sulphur and quicksilver he regarded water and air as the main constituents of matter, while earth merely served as a kind of skeleton. His work represents a curious combination of quantitative and experimental analysis, with neoplatonic, unmechanical, vitalistic and almost anti-rational ideas.[331] He coined the term 'gas', but did not use it in its current material sense but to denote a specific, almost metaphysical

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[325] *ibidem,* 267-268.
[326] *ibidem,* 269-270.
[327] Ball (2006), *The Devil's Doctor*.
[328] *Gutta*, Latin for 'drop', refers to an old wives' tale that stroke is cause by a drop of blood that falls from the head to the heart and thereby stops its action (Nymannus (1629), *Tractatus de Apoplexia*, 6).
[329] Sudhoff, ed. (1931), *Paracelsus, Sämtliche Werke,* volume V, 244*.* Nowadays, the term *synovia* denotes the thick mucous membranes that line the joints; Paracelsus probably had a kind of lubricant in mind. Somewhat later in the text he uses the German word *Altenwachs*.
[330] Pagel (1982), *Joan Baptista Van Helmont*.
[331] Brock (1992), *History of Chemistry*, 49-51.

essence that remained after a substance had been burned.[332] Van Helmont drew attention to the acidity of gastric fluid, attributed a role to it in the process of digestion, but warned that acid could be harmful outside the stomach.[333]

Franciscus de le Boe (***Sylvius***; 1614-1672), professor of medicine at the university of Leiden, introduced chemistry into academic medicine.[334] His student ***Reinier de Graef*** proved through experiments in dogs and calves that pancreatic juice was not a waste product, as Van Helmont had thought,[335] but a useful substance, tasting sometimes insipid but mostly acid.[336] On the other hand bile had been found bitter when tasted, like salts of lye did, so Sylvius and De Graef thought the mixture of the two fluids would lead to a dynamic competition, effervescence, similar to what happens when vinegar is poured on chalk.[337] Sylvius inspired a German physician, Otto Tacke (***Tachenius***; 1610-1680), who studied in Padua and practiced in Venice, to write a small book in which he reduced not only digestion, but also matters of health and disease in general to a battle between two substances, one acid, the other alkaline – as he termed it.[338] The title, *Hippocrates Chymicus*, was intended to symbolise the junction of modern science and ancient wisdom. Galen's hold might be severely on the wane, but the aphorisms and other writings of Hippocrates were often obscure enough to allow borrowing his authority in order to sustain new hypotheses (figure 20).

Figure 20*. Allegorical engraving of Galen and Hippocrates adjoining the tree of wisdom; while Hippocrates reaps fleshy leaves, Galen picks only thorns. From the monograph* De morbo Attonito *('The stunned disease'), a synonym for apoplexy; it was published in 1677, the same year as Bayle's book. The author of the monograph, Justus Cortnumm, born in 1621 in Zelle, Saxony, had died in 1675. He had been professor and dean at the Academy of Sorau, in Saxony (now Zary, at the western border of Poland). His style of dividing the text in a large number of chapters resembles that of Nymannus. Having savaged the hypotheses about the cause of apoplexy proposed by Fernel, Platter and Sennert and hardly referring to Wepfer's work, Cortnumm finds support in Hippocratic texts for his main thesis that the common cause is interruption of the blood flow. He largely avoids the issue where and how this occurs, except that it is beyond the passage of the carotid through the dural membrane.*

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[332] van Helmont (1648), *Ortus medicinae*, 73-81.
[333] *ibidem,* 294.
[334] van Gijn (2001), 'Franciscus Sylvius'.
[335] van Helmont (1648), *Ortus medicinae.*
[336] de Graef (1664), *De Succi Pancreatici*, 17 and 33. In fact pancreatic juice is not acid, as Sylvius expected, hoped and found, but alkaline, or lye-like (*lixivus*), as this property was mostly called in the 17th century. Incidentally, animal lovers will find De Graef's experiments rather hair-raising.
[337] *ibidem,* 22 and 38-40.
[338] Tachenius (1666), *Hippocrates Chymicus*. De le Boe (Sylvius) does not use the term 'alkaline' but opposes acids to 'salts' (De le Boe (1679), *Opera Medica*), while his pupil Cornelis Bontekoe uses the term profusely (Bontekoe (1689), *Alle de Werken*).

Apoplexy and chemistry: Hippocrates to the rescue

This chemical approach was the bandwagon ***François Bayle*** (1622-1709),[339] professor of medicine in Toulouse, jumped upon in his book on apoplexy, published in 1677. With regard to apoplexy he unites the teachings of Hippocrates with recent anatomical discoveries:

> Those who are true disciples of Hippocrates do not enter into speculation of the kind I am talking about before they know the structure of the human body and the function of its parts and especially of the brain; they must acquire all this knowledge, not from books (which Galen himself forbids), but by dissection of the body parts themselves. They have guides to be followed in the excellent men Willis, Malpighi, Steno, De Graaf and others. [....] I will establish the cause of that most violent affliction, with Hippocrates as my guide, with experience as my companion and with reason as my helper.[340]

Bayle is rather limited in following up on his own exhortation. After a long introduction on the clinical features of apoplexy and after an extensive discourse intended to dismiss Galen's theory about thick phlegm in the ventricles of the brain, including Vesalius's account of the hydrocephalic child, he recounts all four case histories in Wepfer's book of 1658, with only minor abridgements. He then dismisses Wepfer's hypothesis about 'compression' as the explanation why local effusions of blood or serum could deprive all nerves from the access of animated spirits, by a circuitous argument about 'pressure', invoking the example of divers.[341] In a next move, he draws attention to his own findings on dissection; these are not related to the brain, but to the heart:

> Others think that carotid arteries are obstructed, at least sometimes, by the bodies that attach themselves to the blood vessels and cardiac ventricles of cachectic persons or of people afflicted by chronic disease. They call these [bodies] phlegm-like, because they are sometimes white and are thought to arise from thick phlegm, but a better term for them is Polyps, owing to their similarity with the tumours of that name that not rarely infest the insides of the nostrils. These bodies sometimes occur in the ventricles of the heart, sometimes in the auricles, as a sort of roots, and extend into the inside of vessels, or sometimes they are not attached anywhere. Twice I was able to find attachments of this kind in the hospital of Toulouse, in two women, one of whom died from dropsy, the other was cachectic; afterwards she gradually wasted away until at last she left life. In both [patients] the bodies were contained in the ventricles of the heart, not attached to any structure, rounded in shape, a bit smaller than a walnut, coloured white, resembling a gelatinous substance. In Paris I observed two polyps in the Charité Hospital in a man of about fifty years. They were dark-red in colour, one extending from the right ventricle of the heart into the auricle, the other from the left ventricle into the aorta; their width was about four lines, the thickness a little more than one line.[342]

Bayle does not forget to cite the clotted blood found in the heart of some of Wepfer's patients (see page 87-88) and in a few other dissections he had summarily heard about.[343] In a final act of an explanation in which the origin of apoplexy is to be sought in the blood rather than in the skull, Bayle brings Hippocrates on the stage. First he emphasizes, with extensive quotations, that the Father of medicine regarded interruption of the blood flow as

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[339] Hirsch (1884-1888), *Biographisches Lexikon* volume VI, 464.

[340] Bayle (1677), *Tractatus de Apoplexia*, 3-4.

[341] *ibidem,* 43-49.

[342] *ibidem,* 57-58. A line is almost 2 mm (https://www.convert-me.com/en/convert/history_length/eslinea.html?u=eslinea&v=1)

[343] *ibidem,* 94-95.

the primary cause of apoplexy.[344] ***Justus Cortnumm***, his colleague from Saxony, based the explanation of apoplexy in his monograph on this same Hippocratic idea, but left it at that.[345] In contrast, Bayle goes on to draw attention to the association of apoplexy with black bile in the Hippocratic writings. As a last step, with many circumstantial arguments, he proposes the acidity of black bile as the factor initiating the clotting process that eventually extends to the brain:

> The main quality of black bile, from which its activity depends most of all, is acidity. When it is moderate, its force lends a moderate consistency to the blood. [Its consistency] is excessive if its quantity is excessive and its acidity is made more acute, especially if it additionally has harshness and acerbity; for then it has considerable power to halt the blood. Indeed, this is testified by experience: blood outside vessels on which acid has been poured congeals more easily; also serum that has been separated from blood, liquid and clear like water, coagulates in the same way if acid is poured on it. But the same clotting can be brought about if acid fluids are discharged inside vessels. Since acids obtain that power, it is therefore obvious that if black bile, collected in some body part and made too acid, is moved from there and passes into the mass of blood, it can cause local coagulation, repress the movement of spirits and impede their production. If that collection of too acid black bile and its effusion in the blood takes place in the brain, the production and inflow of spirits there will unavoidably diminish or completely shut down, depending on whether the quantity was greater or smaller and the degree of acidity or acerbity higher or smaller.[346]

Incidentally, Bayle was to some extent a Cartesian, at least in his perception of the relationship between body and mind, when he was asked for advice in the controversial issue of witchcraft and possession by the devil.[347]

No exit for 'excrements' of the brain

Before leaving the 17th century, I should come back to an unfinished side issue. Vesalius and Varolio, as I have shown (pages 43-45), thought that the fluid from the ventricles dripped down via the bottom part of the third ventricle or funnel (*infundibulum*), to the pituitary gland and from there to the nasal cavities and the palate. Varolio had an extra reason, since he proposed that the ventricles had no role in the production and transport of animated spirits; in the teleological mood inherited from Aristotelian philosophy he assigned another purpose to the ventricles, as a sewage system for excrements from the brain. This argument remained popular, also with many physicians in the 17th century, including Cortnumm.[348]

However, in 1655 and 1660 Conrad Victor Schneider, professor of medicine at Wittenberg, successor of Sennert and Nymann, published careful studies of the skull base and proved that fluid could not pass through it, especially at two sites often mentioned: firstly the cribriform (sieve-like) bone (figure 21, A, next page),[349] secondly the horse's saddle (or Turkish saddle; figure 21, B, next page), where the pituitary gland lies buried. Schneider wrote:

[344] *ibidem,* 61.
[345] Cortnumm (1677), *De morbo attonito*, 84.
[346] Bayle (1677), *Tractatus de Apoplexia*, 87.
[347] Easton (2011), 'Francois Bayle'.
[348] Cortnumm (1677), *De morbo attonito*, 58.
[349] Schneider (1655), *Liber de Osse Cribriformi*.

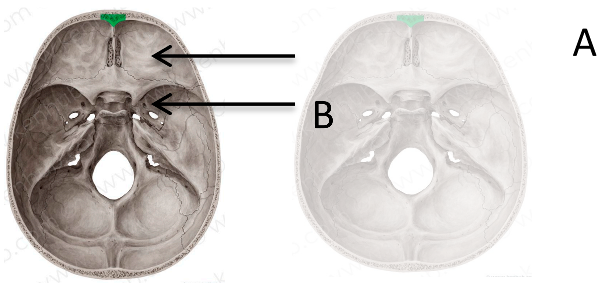

Figure 21. *Modern illustration of the base of the skull, seen from the inside (same as figure 17). A = cribriform or sieve-like bone. B = pituitary fossa (or Turkish saddle), normally containing the pituitary gland.*

> I say that the pituitary gland does not contain the channels Vesalius thinks up. [....] Most people join me in denying that a part of this bone has ever been truly and normally perforated. [....] I have found out and investigated that all fluid infused at that site stays put and forms a kind of pool. [....] And through those openings it can in no way flow to those cavities and to the palate.[350]

So Schneider relegated the idea that secretions from the nose and the throat were waste material from the brain to the realm of fiction. Remarkably, he used an experiment with fluid to prove his point. Willis cited him with approval,[351] while Wepfer had more or less predicted his findings:

> For if we think of those fluids that most people, including healthy persons, daily blow from their nose or otherwise get rid of, fluids usually believed to be natural and normal waste products of the brain, or if we look at catarrh, in other words a more copious production of these fluids, we realize that they are expelled by none of these pathways or openings. For the visible openings in the base of the brain are intended for either the exit of nerves, spinal cord and lateral sinuses, or for the access of the carotid and vertebral arteries, as well as those [vessels] that are distributed over the thick membrane.[352]

A synthesis in 1709

Herman Boerhaave (1668-1738), in 1709 appointed professor of botany at the University of Leiden, on his way to become one of the most famous physicians of his time, published in the same year a slender volume in octavo format with a summary of the art of diagnosis and treatment in medicine. I briefly referred to the book in the introduction to this thesis, where I cited Boerhaave's opinion that all knowledge on the subject of apoplexy was the result of the observation of patients and corpses (page 9). In fact in the course of his academic education Boerhaave had been converted from a firm belief in reasoning from first principles to the conviction that progress science depended on information from the senses.[353] The book was divided in a number of chapters, but paragraphs were consecutively numbered and entitled 'Aphorisms', a bold title by which Boerhaave plainly showed his intention to become a modern Hippocrates.

In aphorism 1007 he announces the subject of apoplexy, in the next one he lists the clinical features, by now well-known to the reader. Nevertheless I reproduce them, not only provide an introduction to Boerhaave's terse style, but also to show that the definition has not appreciably changed from what was culled from Galen's writings 150 years before:

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[350] Schneider (1660), *Liber primus de Catarrhis*, 239-240.
[351] Willis (1664), *Cerebri anatome*, 56.
[352] Wepfer (1658), *Observationes Anatomicae*, 153.
[353] Cook (2007), *Matters of Exchange*, 383-394.

> 1008. This [apoplexy] is said to be present when suddenly the actions of the five external senses as well as the internal sense and all voluntary movements are suddenly abolished, while the pulse is preserved, mostly [even] strong, as well as a difficult, deep and snoring respiration; it is just like the image of a deep and permanent sleep.[354]

If there is a change at all, Boerhaave omits the collapse or the fall to the floor, which is the cardinal and initial feature mentioned in the ancient descriptions. This posture may be implicitly indicated by the comparison with sleep, yet it is almost the only feature that can be called an observation. All the rest is guesswork about the separate actions of the nervous system that are defective: the patient cannot feel, see, hear, smell or taste, cannot think and cannot move – except with regard to breathing and heart action.

In aphorism 1009 Boerhaave further elaborates on this explanation by pointing out that some causes result in a blockade, within the brain, of the traffic of spirituous fluids between the organs for sensation and motion on the one hand and the 'centre of thinking' (*sensorium commune*) on the other. A similar spirituous fluid for the cerebellum was still available, Boerhaave supposed, following Willis, and served to sustain breathing and heart action (the term 'fluid' implies he had discarded the possibility that spirits were vaporous in nature).

In a third phase of interpretation, Boerhaave goes on to list the observable, material causes that can be responsible for such a blockade. His first category consists of certain physical attributes that present physicians would call 'predisposing factors' rather than actual causes, but I reproduce these nonetheless. Following each of the subsequent material causes he adds a long list of symptoms, signs or circumstances that might identify the cause in question; I will represent these indicative features by a single word.

> 1010. All causes that have been enumerated by Observers can be reduced to a few categories, for the convenience of practice:
>
> 1. The inborn structure of the body: a large head; a short neck, often consisting of only six vertebrae; a vast and obese body; a plethoric constitution in combination with a phlegmatic disposition.
> 2. Whatever changes blood, lymph or the substance of spirits in such a way that they cannot freely travel through the arteries of the brain, but get stuck. Such are:
>   a) Polypous concretions in the carotid and vertebral arteries, originated primarily around the heart or in the skull itself. [*indications*]
>   b) Inflammatory clotting of blood. [*indications*]
>   c) A nature of the whole of the blood that is glutinous, phlegmatic and slow. [*indications*]
> 3. Whatever compresses the arteries themselves or the nervous channels of the brain in such a way that the blood and the spirits cannot pass:
>   a) Plethora, an overfilled constitution. [*indications*]
>   b) Any kind of tumour arisen in the head: inflammatory, abscess-like, serous, phlegmatic, fat-like, scar-like or bony, compressing either arteries or the confluence of veins around the torcular, or the medullary beginnings of the nerves.
>   c) Too great a velocity of the blood contained in the head, such as by a blocked pathway to [branches of] arteries downstream.
>   d) [Factors] outside the skull that compress the veins carrying the blood away from the brain.
>   e) Effusion of fluids outside the hard or the tender membrane: blood, pus, a wound, or lymph.

[354] Boerhaave (1709), *Aphorismi de cognoscendis et curandis morbis*, 248.

4. Everything that dissolves the arterial, venous or lymphatic vessels at the inside of the brain in such a way, that the fluid passes out, accumulates and through its pressure damages the curved origins of the cranial nerves. Such fluids are: serum in patients with dropsy or a dropsical diathesis; blood in plethoric patients; acid black bile in melancholic patients; scorbutic patients or those with gout. [*indications*]
5. Some [authors] cite poisonous vapours in this regard; however, these act either via the three factors last mentioned (2, 3 and 4), or they damage primarily the lung rather than the brain.[355]

Actually, Boerhaave does not refer to any experience of his own, stays on the fence and resorts to a compilation of almost everything he has encountered in his readings, including speculative events not supported by even a single observation in the literal sense of the word, such as overfilling of brain vessels or blockade of veins (including Nymann's torcular). A similar catalogue of causes can be found in a monograph on apoplexy that appeared in the same year as Boerhaave's 'aphorisms', written by a professor of medicine in Pisa.[356] To diminish the multitude of causes, Boerhaave closes the section on apoplexy by simplifying his list as follows:

> 1012. From these [categories] it emerges that this disease is often caused by different and even opposite causes. Thus they can be properly divided in sanguineous and phlegmatic; but this division is not perfect, because there is also a serous, a melancholic, a polypous, etc. [apoplexy].[357]

This attempt at reducing the number of possibilities by listing different fluids would, in the course of time, prove less fruitful than the main categories of his long list, with the exception of predisposing factors such as a short neck, as well as of the vapours Boerhaave had already discounted himself. This leaves the following three categories: in the first place occlusion of arteries, secondly [sudden] compression of the brain from within or without, and thirdly rupture of vessels of the brain.

Wepfer, supported by Willis, had defined these three main categories of apoplexy on the basis of post mortem observations in combination with details of the patient's history, and with the help of Harvey's theory of the circulation of blood. Yet, by 1700 apparently many old notions lingered on and much remained to be explained. Eventually occlusion as well as rupture of blood vessels would turn out to be the core events in apoplexy, while 'compression by serum' would prove one of the many dead alleys in science that one only finds by starting at the beginning.

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355 *ibidem,* 249-253.

356 Mistichelli (1709), *Trattato dell' Apoplessia*, 51-53. This book is the first monograph on apoplexy in a vernacular language. Mistichelli proposed application of a branding iron to paralysed body parts in some cases of apoplexy (*ibidem,* 121-125).

357 Boerhaave (1709), *Aphorismi de cognoscendis et curandis morbis*, 253.

Chapter 7

CONCLUSION

The art of observation, in six steps

The scientific revolution

In this concluding chapter I will at first look back on the developments in the methods of observation that physicians used to understand the pathogenesis of apoplexy. I will then attempt to view these developments within medicine against the background of the momentous changes occurring within science in general, the so-called scientific revolution.

Of course the story of apoplexy actually begins with the gradual emergence of a definition of this disease: an unexpected collapse, accompanied by loss of sensation and motion and distinguished from death by the preservation of breathing and heart action. Unavoidably it had taken much time and thought before these different phenomena had been recognised as a more or less coherent pattern, as a meaningful cluster of symptoms. It is at this stage, when the disease had been to some extent defined by Galen and his description had been retrieved as well as accepted by physicians in the middle of the 16th century, that my study took off.

The art of observation, in six steps

In my analysis of the observational methods that were used to understand the causes of apoplexy I have tried to distinguish these developments into six separate phases. The premise underlying the construction of any division at all is that 'observation' is not an all-or-nothing phenomenon.

Clinical observation: one- or two-way traffic?

First of all, the word 'observation' has not always had the same meaning. 'To observe' may also imply a form of obeisance, or 'observance', in the sense that what the observer sees, hears or otherwise perceives constitutes the recognition and confirmation of something he already knew and perhaps even expected. In that sense the term 'observation' does not evoke the currently common ideal of a one-way traffic of information from object to investigator; instead, it represents a much more interactive process. Pomata has argued that in the period between 1500 and 1650 'observation' has 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, disciplines that were to some extent interrelated at the time.[358]

It is in the modern sense of the word that *observationes* or *curationes* became popular in the medical world of the late 16th century: case records of patients, in which phenomena are described, followed by explanatory notes referring to the corresponding theory (*scholia*). This method of presentation, first applied in medical teaching in Northern Italy, became the template of published case records by Amatus Lusitanus and several others (see page 20).[359] But it is not easy to isolate details, or to disengage perceptions from theories, as shown by the only example of apoplexy in the collected records of Amatus Lusitanus:

> The daughter of a woodworker, eleven years old, fell victim to apoplexy within an hour of having her head washed. She was a fat girl, with a beautiful face and very sanguineous. When she was seized by the attack she grunted very strongly and suffered from violent shaking of the limbs. On my speedy arrival I ordered to restrain [the abnormal movements] by means of traction, ligatures, frictions and application of cupping glasses, on rather deep scratch

358 Pomata (2011), 'Observation Rising', 47-54.
359 *ibidem,* 54-60.

> wounds. But when the symptoms persisted, I ordered to decrease [the amount of] blood by cutting an exterior vein of the arm, which was much swollen at that moment. And because outside Spain all Physicians are afraid of venesection below the age of fourteen years, ingrained by a decree of Galen, they were unable to follow my advice. Therefore, knowing that this apoplexy, called the stunned disease by Cornelius Celsus in chapter 26 of his 3rd book on medicine, was a strong one, I departed, since (as he says) hopeless cases have to be given up, with nothing else than the prognostic message. Yet the girl survived the paroxysm on that occasion, though not without harm, since she was affected by a complete paralysis, or loss of power, on the right side; she was entrusted to other physicians and met her end within a month.[360]

I wish to avoid the issue whether this attack should, in retrospect, be called apoplexy or epilepsy (Galen attributed both conditions to obstruction of the cerebral ventricles). The point I wish to make is that the style of the clinical description is still undeveloped, apart from the intrusion of theory (both Galen and Celsus make their appearance). It contains speculative elements ('sanguinous' implies a relatively large amount of blood, probably derived from the colour of the patient's face), while its brevity leaves several questions unanswered. For example: did all four limbs show convulsive movements, given that only the right side later became paralysed? And which features made Amatus regard the apoplexy as a severe one, beyond hope?

Relating the phenomena of disease with findings in the brain

So, recording of clinical facts is an art that has to be learned, not just in a lifetime but in the course of several generations. The same applies to recording anatomical abnormalities in the brain in cases of apoplexy with a fatal outcome – the anatomy of disease. As I have shown above, this started with a mere glance and ended with meticulous dissection. It is only the combination of clinical and pathological characteristics, in progressive detail, that has led to an improved understanding of apoplexy.

It is for this reason that I have arranged this dual development in six discrete stages. Admittedly, there is some overlap in time as well as in content; therefore this ordering may be regarded as a somewhat artificial fashion to describe a continuous process of advancing discernment. Yet I feel there is sufficient justification for these divisions, even apart from their anchoring function. Finally, perhaps these stages can be used not just with regard to a single disease, apoplexy, but for the discipline of medicine as a whole, at least in the period between 1550 and 1700.

1. Opening the skull

This first step is perhaps the most momentous one: the decision to try and have a look at the brain of a patient who has succumbed to apoplexy. The procedure faces practical and moral obstacles (see page 18), so it must be prompted by doubt. Up to the middle of the 16th century doubt was scarce:[361] physicians were generally satisfied with interpreting the clinical phenomena in terms of what Galen had written about it: overstuffing of the cavities of the brain by phlegm. As I showed in chapter 4, the first port mortem investigations were sometimes motivated or at least influenced by judicial arguments, when crime was suspected. But in some of them it must have been doubt or, as some say, curiosity – a word that mirrors doubt, only in a more positive way.

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[360] Lusitanus (1560), *Curationum Medicinalium*, 235-236.

[361] Gulczynski, et al. (2009), 'Short history of the autopsy. Part I'.

Questioning Galen is a bold step indeed. For in the same way as early humanists like Francesco Petrarca welcomed the end of 'dark ages',[362] early physicians like Fernel felt they were part of a medical Renaissance in which their art had only recently come to life again, thanks to the restoration of ancient Greek wisdom, purged from barbarisms and with pristine splendour (page 23).[363] These ancient medical texts, almost matching the Bible in age and written in peremptory style, had a status far transcending the fact that they were actually based on observations that anybody could repeat and check. Their contents were almost universally regarded as almost abstract 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 in lines and angles.[364] What is more, the synthesis between Aristotelian natural philosophy and Christian theology that had been crafted in the 13th century by Thomas of Aquino and few others endowed the Greek heritage with an almost religious supremacy,[365] so that any censure or objection might be felt to border on heresy.

The first reports in which physicians inspected the brain of victims of apoplexy were not very informative. In the first place, their lack of detail revealed that the inspection could not have been more than a quick look (pages 39-41): blood at the base of the brain, or ventricles of the brain filled with blood or with aqueous fluid (two patients). Secondly, in one of these four patients external violence had preceded the disease, in the other three there was no information at all about the clinical phenomena.

Similarly, Varolio's almost casual argument that he had witnessed dissections of patients with apoplexy in which the ventricles contained "no greater quantity of excrements [I.e. fluid] than one usually finds in all others" was not supported by information about events or the patients' symptoms before death. Again this finding, in fact potential world news in medicine but apparently suppressed because it did not agree with the ancients, cannot be properly interpreted through the lack of corresponding histories.

2. Handling and exploring the brain as an object

Varolio's name is solely remembered by medical students – if at all, because eponyms are getting out of fashion – by his description of a prominent structure at the base of the brain he called 'the bridge' (*pons*). Actually he deserves to be remembered especially by the dissection technique he developed for freeing the brain from its connections, so that it could be taken out of the corpse.

This new technique had not only practical advantages but above all philosophical, yes almost metaphysical consequences. Until then the brain, considered the seat of reason but also of morality, had remained part of the corpse as a whole, of the person almost. Vesalius had, in his famous *Fabrica* of 1543, usually illustrated the brain as part of at least the head, apart from a single and fairly inaccurate illustration of the base of the brain. By removing the brain, despite its soft and limp texture, in its entirety from the body, like the heart, the lungs, the spleen or other organs, Varolio opened it up for inspection and dissection, with regard to normal anatomy as well as to the anatomy of disease.

Varolio's thesis that it was the substance of the brain and not its cavities that formed the vehicle for the 'animated spirits', was supported by his anatomical arguments (most

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362 Mommsen (1942), 'Petrarch's 'Dark Ages'', 234-242.
363 Fernelius (1548), *De Abditis Causis*, 2.
364 Dijksterhuis (1950), *Mechanisering*, 54-58.
365 *ibidem,* 141-143.

nerves originated near the smallest part of the ventricular system; page 45), by his teleological argument that a storage site was needed for the secretions filling the nose and throat; page 51), but especially by reports of two other physicians, about abnormal brains in combination with clinical information.

3. Brain dissection combined with clinical information

Vesalius and Fabry had each dissected a child with exceedingly large ventricles. Both children had died at the age of around two and a half years (pages 47-50). The vital piece of clinical information, though sparse, was that both children had shown movements of their limbs and that they had shown 'sensation' in the sense that they had interacted with their parents even at a stage in which their cerebral ventricles were abnormally large and apparently occluded.

These two case reports with dual information, about the patients' behaviour and about the anatomical abnormalities of the brain, were often cited by contemporaries and later generations because they represented the last nail in the coffin of the notion that the cerebral ventricles were essential for the production and transport of animated spirits.

4. Dynamic processes studied in live creatures

William Harvey's discovery of the circulation of blood (Chapter 5) may have been inspired by an analogy with the orbiting of the sun and planets, as conceived at the time, but he supported his hypothesis by careful inspection of heart movements in live animals, whose chest had been opened: the auricles contracted slightly earlier than the ventricles, and only a little later the large arteries expanded. Also he calculated the impossible quantity of blood that the liver would have to produce if indeed all expulsions of the heart were consumed by muscles and organs, as the ancients believed.

Also Harvey proved experimentally, by means of ligation experiments in animals and also in the upper arm of a live person, that blood moved away from the heart in arteries and towards the heart in veins.

It hardly requires further comment how important the discovery of the movement of blood was for the understanding of apoplexy. The route of circulating blood through the brain, from arteries to smaller branches, then on to veins and sinuses, immediately cancelled out clever conjectures about obstruction at a strategic site in the system of venous sinuses (pages 55-57). Instead, the force of pulsating blood would provide explanations for apoplexy that were unheard of before.

5. Patient collection of facts: disease manifestations and brain abnormalities

The autopsy reports of Wepfer constitute a culmination of the art of the clinico-pathological correlation: not only the brain of the patient is taken out and dissected in detail, also the symptoms the patient showed at the onset and in the course of the disease are retrieved by interviewing relatives and bystanders. It is only in the context of the different events while the patient was still alive that abnormalities found in the brain can acquire their meaning.

The importance of Wepfer's method of meticulous reporting lies in the separation of observation and interpretation. This is a lesson that has to be learned and re-learned by every medical student up to the present day; its importance can hardly be underestimated. For example, a patient telling the doctor she 'feels ants crawling under her skin' should be recorded as feeling ants crawling under her skin, not as 'having paraesthesia'!

A striking example is Wepfer's accounting of the three patients whose disease he eventually interpreted as 'serous apoplexy'. The very precision of his descriptions, with essential details such as preceding lung disease in all, a preceding hemiplegia in the two young women, followed by a final episode of weeks with increasing headache but no fever, with blindness in the male patient, allows recognition of tuberculous infection of the brain, currently almost extinct in the industrialised world.

6. Experiments

I already mentioned Harvey's ligation of major blood vessels in live animals – regrettably without the measures to reduce suffering available today – as well as his ligation of veins in the upper arm of a healthy person to show how valves ensured that venous blood moved towards the heart. Also I should like to recall Wepfer's use of a probe to make sure that the four large arteries to the brain were indeed interconnected, and Willis's injection of ink-stained fluid to test the patency of these same connections (page 95). Finally, Schneider poured fluid at the inside of the skull base to prove that the small holes in the cribriform bone permitted only nerve fibres for the sense of smell and nu fluid, and that the floor of the pituitary fossa was completely impermeable (pages 100-101).

Improved observation even in the 20th century: 'loss of senses' redefined

Was the art of observation complete by 1700, apart from the later development that experiments and instruments would come to include the invisible natural world, so defying the term 'observation' and requiring abstract methods for dealing with the infinitely small and the infinitely large? Not quite. Verbal descriptions of abnormalities of the human body would be supported by illustrations: initially engravings, later lithographs and photographs.

But also the verbal description of symptoms required further refinement. For example, in the 19th century loss of speech in apoplexy would be recognised as a disorder of the brain rather than paralysis of the tongue. And it would not be until the end of the 20th century that a solution was found for the thorny problem of 'loss of senses' that formed an essential element in the definition of apoplexy. The main part of the problem is that the term does not represent an actual observation, but an interpretation: "the patient does not react, so he must have lost his senses." The modern term 'unconsciousness' has the same disadvantage: consciousness cannot be seen, only manifestations of its presence or absence. In short, the words 'senselessness' and 'unconsciousness' do not represent actual perceptions, not something that can be photographed or filmed: the terms are merely conclusions of the observer's mind about what is wrong in the patient's brain.

A second problem with 'senses' and 'consciousness' is that one is not dealing with an all-or-nothing phenomenon. Depending on the nature and the strength of stimuli, patients may or may not respond, or just a little. This has led to a plethora of terms for describing different stages of unconsciousness: somnolence, lethargy, stupor, carus, coma and semi-coma, to name the most common categories. In 1974 Scottish neurosurgeons came up with a simple solution. Recognising that the interpretation 'unconsciousness' represents the observation 'unresponsiveness', they defined three modes of reaction to stimulation, by sound or touch: opening of the eyes, movements of the arm and verbal response.[366]

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[366] Teasdale and Jennett (1974), 'Assessment of coma'. For each criterion there are four or five gradations. An example: E2 (opens eyes after painful stimulus), M3 (withdraws arm after painful stimulus), V2 (grunts, without speech). The scale is ordinal, not numerical: numbers represent a grade rather than a standard value; therefore the numbers should not be added, let alone averaged.

Post mortem observations require energy and persuasion

Curiosity is not enough. The request of physicians to obtain permission for autopsy was and is still met by hesitation and even resistance of relatives. The common notion, in medical and lay circles alike, that modern imaging methods have made post mortem dissection almost superfluous is repudiated by recent reports that in almost 30% of cases the autopsy produces pivotal or at least major new information.[367]

Johann Jakob Wepfer used his network of nobility and clergy to obtain permission to perform dissection in the four patients with apoplexy he described in 1658 and of two others in 1675. He had also secured the cooperation of the senate of Schaffhausen, for which assistance he expressed profuse thanks in his preface of the 1658 book:

> Anatomists bestow even more glittering honour on this dwelling of the divine image and abode of the Holy Ghost,[368] when they openly display any part of our body by skilful dissection. In doing so they admire the indescribable wisdom and immeasurable goodness of God. At the same time they teach in which way the health of those alive (by far the most important of all benefits that humans can obtain in this world) can be preserved - or restored if it has been lost. It seems as if this good fortune to entire Mankind is begrudged them by those who, led by whatever religion, maliciously proclaim that any Corpse must be buried intact, while they themselves are destined to become food for worms. They exert themselves as much as they can to forbid it, so that people who were good for nothing during life are also of no use when they are dead. The task may be foul and for some it may seem repulsive to drench one's hands in blood and gore, but this filth can be rinsed off with a little water. More repulsive and despicable than anatomical material is ignorance, which breeds a disgrace to Physicians and Surgeons that neither the Rhine nor the Ocean can wash away.[369]

The scientific revolution

The chosen period, between 1550 and 1700, coincides with important developments in the history of science in general. Critical events took place, not merely in medicine but in many other disciplines: mathematics, astronomy, physics, geography, and economy. At the end of this period the natural world, traditionally conceptualised in abstract terms, came to be described in materialistic or even atomistic terms, through application of mathematical principles, mechanical notions or experimental methods; purpose as a guiding principle was replaced by necessity.[370] For this reason the era has often been called that of the 'scientific revolution', a historiographic notion developed in the 1930s.[371]

This periodization has not escaped criticism.[372] Among the arguments questioning its validity are the limited time span (for example, some would like to include Lavoisier), its 'internalist' narrative, which fails to take account of societal factors such as Puritanism, capitalism and technology, and – unavoidably – the completely different way in which the natural world has been conceived and studied in the past, compared with modern times.[373] On the other hand, "many key figures in the late sixteenth and seventeenth centuries vigorously expressed their view that they were proposing some very new and very important

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[367] Tavora, et al. (2008), 'Discrepancies between clinical and autopsy diagnoses'.
[368] Refers to the *Heiliggeistspital* in Schaffhausen; apparently an image of physicians was painted on a wall.
[369] Wepfer (1658), *Observationes Anatomicae*, * 5-6.
[370] Dijksterhuis (1950), *Mechanisering*; Cohen (2010), *How Modern Science came into the World*.
[371] Cohen (2010), *How Modern Science came into the World*, xvii.
[372] Park and Daston (2006), 'The age of the new', 13.
[373] Cunningham and Williams (1993), 'De-centring the big Picture', 413-414.

changes in the knowledge of natural reality and in the practices by which legitimate knowledge was to be secured, assessed and communicated."[374] In addition, one can hardly contest, not only that scholarly scientific traditions and beliefs based on ancient sources were gradually eroded in this period by the idea that the boundaries of knowledge were not finite but could be opened up with the help of careful observations, calculations and experiments, but also that the story of these changes deserves to be told.

Fact-finding

With regard to the life sciences and the 'Scientific Revolution', the comment has been made that they do not fit the mould of mathematization and mechanistic thinking.[375] Indeed they don't, but Cohen, in his detailed reconstruction of that same period, attributes the emergence of science in its modern sense to more than that. He describes the existence, then the expansion and finally the convergence of three fundamentally different methods for acquiring nature knowledge: not only the philosophical, abstract ('Athenian') mode and the mathematical ('Alexandrian') mode, but also systematic observation and fact-finding (the mode of 'coercive empiricism').[376] It is this third mode for obtaining nature knowledge that applies to biology and medicine.

So, the method of observation and record keeping without interpretation, developing in a step-wise fashion in physicians of the 16th and 17th century, is what represents the contribution of medicine to scientific thinking. This patient collecting of facts mirrors the attitude of the earlier botanist Carolus Clusius (Charles de l'Écluse; 1526-1609), who was more concerned with the exact description of plants than with their hidden forces; it "was the particulars that counted, not the general principles".[377] Of course Wepfer and Willis, the most prominent representatives from the final part of the period I studied, at least for the subject of apoplexy, offered their own interpretations. Some of these are no longer valid, but these interpretations and theories have been kept apart from what they actually saw.

Communication

Unbiased minds are not the whole story. Physicians did not think and write in a vacuum. They were part of a larger community, spanning the continent. As I recounted above (pages 15-16), young physicians who had ambition as well as the support of a prosperous family or benefactor increasingly often travelled to universities with a reputation of excellence in teaching, even if the geographical distance was nearly prohibitive. It was the Latin language that united learned communities far apart – until its advantage was sacrificed by the nationalism of the 19th century, a loss that the ubiquity of English in our own time would only slowly atone for. The pivotal role of the universities in Northern Italy in the diffusion of medical knowledge by personal contacts is exemplified by the diffusion of Varolio's method of studying the brain and his conception of brain tissue conveying the animated spirits. It travelled from Bologna first to Padua and from there to Basle (Bauhin, who copied Varolio's views and even his words and figures in his own popular textbook and who must have informed his senior colleague Platter).

A second, even more important component of communication is reading. The sharing of medical knowledge owed a great deal to the growing book culture. In the course of the 16th

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[374] Shapin (1996), *Scientific Revolution*, 5.
[375] Cunningham and Williams (1993), 'De-centring the big Picture', 413.
[376] Cohen (2010), *How Modern Science came into the World*, 113-141.
[377] Cook (2007), *Matters of Exchange*, 104 and 131.

century printing presses appeared in all major cities and most university towns of Europe. Initially the medical books the publishing firms turned out were for the most part textbooks from academics, covering the whole of medicine (pages 19-20). Gradually the public at which medical publications were pitched would include not only students but also practicing physicians. Increasingly, practitioners outside universities were also the authors; their readers were interested in experiences of their colleagues. Wepfer's book of 1658 was published in Schaffhausen but reached Willis in London and Bayle in Toulouse. Other books might consist of isolated case histories from personal experience or from correspondents, published in serial form, or they might be selected from previous publications. So, in the course of time physicians increasingly took notice of the opinion of colleagues in their own time, as reflected in citation practices. Useful knowledge should no longer be sought only in ancient writings – it could be heard from a colleague, or found in recently published books.

That the new fashion in which the book culture caused new information to travel between contemporaries was not just a matter of convenience, or an interesting social phenomenon. In combination with the developing 'art of observation', it generated a fundamental change in the dynamics of the understanding of nature. As long as communication between physicians revolved around the interpretation of ancient Greek or Arabic writings, the body of knowledge remained essentially static. But as soon as physicians accepted that existing explanations of diseases as well as of the structure and function of the body was incomplete, each new addition to the knowledge base became the point of departure for yet another new element, a process of positive feedback that gained more and more momentum as the number of participants increased.

The pathways of communication between 'new scientists' have often coincided with those between commercial partners, and "the beginnings of a global science occurred during the period of the rise of a global economy".[378] As Cook argues, this intertwinement in time and place has not been a matter of chance but of interaction, prompted by shared interests. For example, the senate of the Republic of Venice, by appointing famous professors from far and wide at its university in Padua, sometimes against conservative opposition,[379] have contributed to the development of European medicine as a whole.

To epitomise, because several physicians in the period between 1550 and 1700 gradually opened their minds to recording what they actually saw instead of trying to recognise the knowledge they had been brought up with, because they valued, in the cause of time, 'how-questions' over 'why-questions', and because they increasingly compared their own findings with those of their contemporaries instead of the texts of ancient writers, I feel justified in calling this period an era of revolution in medicine.

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378 *ibidem,* 416.

379 *ibidem,* 412.

APPENDIX: TRANSLATIONS FROM LATIN

List of original Latin texts cited in this thesis; these have been transferred to the USB stick accompanying this thesis. For the few citations from ancient Greek texts I have used existing translations, as indicated in the main text. In the majority of Latin texts I have translated only parts, though almost invariably the translations are more extensive than the citations I reproduced. The USB stick contains the texts listed below in alphabetical order, as they appear below; in each document my translations are reproduced on facing pages. The text of the thesis is also included, in pdf-format.

Amatus Lusitanus, *Curationum Medicinalium Centuriae II Priores* (Lugduni, 1560). [pages 235-236]

Bauhinus, C., *Theatrum Anatomicum, novis figuris aeneis illustratum et in lucem emissum* (Francofurti, 1605). [pages 695-698]

Bayle, F., *Tractatus de Apoplexia, in quo huius Affectionis Causa penitus inquiritur & curatio exponitur* (Tolosae, 1677). [pages 1-109]

Boerhaave, H., *Aphorismi de Cognoscendis et Curandis Morbis in Usum Domesticae Doctrinae Digesti* (Lugdunum Batavorum, 1709). [pages 248-253]

Cardanus, H., *In Septem Aphorismorum Hippocratis Particulas Commentaria* (Basileae, 1564). [page 727]

Donatus, M., *De Medica Historia Mirabili Libri Sex* (Mantuae, 1586). [page 59v]

Duretus, L., *Hippocratis Magni Coacas Praenotiones* (Parisiis, 1588). [page 366]

Fabricius, G., *Observationum et Curationum Chirurgicarum Centuriae* (Lugduni, 1641). [pages 25-26]

Fernelius, J., *De abditis rerum causis* (Parisiis, 1548). [pages 2 and 267-268]

Fernelius, J., *Medicina* (Lutetiae, 1554). [fragments from *Physiologia*, pages 75-192]

Fernelius, J., *Medicina* (Lutetiae, 1554). [fragment from *Pathologia*, page133]

Forestus, P., *Observationum en Curationum Medicinalium ac Chirurgicarum Opera Omnia* (Rothomagi, 1653). [volume X, pages 505-533; this volume first appeared in 1590]

Harveius, G., *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (Francofurti, 1628). [pages 41-42]

Hofmann, C., *Institutionum medicarum libri sex* (Lugdunum, 1645). [pages 430-432]

Lycosthenes, C., *Prodigiorum ac Ostentorum Chronicon* (Basileae, 1557). [pages 640-641]

Mistichelli, D., *Trattato dell' Apoplessia, in cui con nove Osservazioni Anatomiche, e Riflessioni Fisiche si richercano tutte le Cagioni, e Spezie di quel Male, e vi se palesa frà gli altri un nuovo, & efficace Rimedio* (Roma, 1709). [preface, pages 12-14, 51-53 and 57-59]

Nymannus, G., *Tractatus de Apoplexia* (Wittebergae, 1629). [dedication, preface and pages 1-197]

Paracelsus – see Sudhoff.

Piso, C., *De Praetervisis hactenus Morbis Affectibusque praeter Naturam, ab Aqua seu Serosa Colluvie & Diluvie Ortis* (Ponte ad Monticulum, 1618). [pages 89-90]

Platerus, F., *Praxeos, seu de Cognoscendis, Praedicendis, Praecavendis Curandisque Affectibus Homini Incommodantibus. Tractatus de Functionum Laesionibus.* (Basilae, 1602). [fragments of pages 13-34]

Platerus, F., *Observationum in Hominis Affectibus plerisque, corpori & animo, Functionum Laesione, Dolore, aliave Molestia & Vitio Accomodantibus, Libri tres.* (Basilae, 1614). [pages 14-15 and 407]

Pratensis, I., *De cerebri morbis* (Basilae, 1549). [pages 420-441]

Schneider, C.V., *Liber primus de Catarrhis, quo agitur de Species Catarrhorum, & de Osse Cuneiformi, per quod Catarrhi decurrere finguntur* (Wittebergae, 1660). [pages 220, 239-241]

Sudhoff, K. (Ed.), *Theophrast von Hohenheim gen. Paracelsus, Sämtliche Werke* (München und Berlin, 1931). [volume V, part of page 244]

Varolio, C., *De Nervis Opticis, nonnullisque aliis praeter Communem Opinionem in Humano Capite Observatis ad Hieronimum Mercurialem* (Patavii, 1573). [complete, with response of Mercuralis and rebuttal of Varolio]

Vesalius, A., *De Humani Corporis Fabrica Libri Septem* (Basilae, 1543). [page 4 of dedication; legend on page 621]

Wepfer, J.J., *Observationes Anatomicae ex Cadaveribus eorum, quos sustulit Apoplexia, cum Exercitatione de eius Loco Affecto* (Schaffhusii, 1658). [complete: 304 +xi pages]

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Willis, T., *Cerebri anatome, cui accessit Nervorum descriptio et usus* (Londini, 1664). [pages 93-95]

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De le Boe, F., *Opera medica, tam hactenus inedita, quàm variis locis & formis edita; nunc verò certo ordine disposita, & in unum volumen redacta, cum duplici indice Librorum & Capitum, operi praemisso, altero Rerum, ad calcem adjecto* (Amstelodami, 1679).

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