

The Evolving Concepts of Apoplexy and Brain Softening

Olivier Walusinski

Abstract: Paralysis, affecting motion or sensation, is a condition known from immemorial time. Apoplexy was the generic term used to indicate its cerebral origin until Wepfer established a correlation between apoplexy and cerebral haemorrhage in 1658. During the 17th and 18th centuries, its pathophysiology was discussed, and several hypotheses were suggested, but it was only during the 19th century that cerebral ischaemia and infarction concepts appeared and became recognised as the more prevalent form of stroke. This chapter deals with the history of the emergence and acknowledgment of cerebrovascular brain insult's physiopathology.

1. Early Concepts

Stroke has been recognised and described since ancient times, when it was included within the larger syndrome known as apoplexy. In 1721, Hélié Hélian (1658–?) gave this definition: “Apoplexy is a permanent, sudden numbing and affects organs under voluntary control, resulting in loss of feeling and movement whereas the pulse and breathing remain nearly in their natural state” [1]. The German Johann Jakob Wepfer (1650–1695) established the first correlation between apoplexy and cerebral haemorrhage in 1658, after having described the carotid siphon (Figure 1) [2]. In addition, he sketched out a pathophysiological framework by referring to arterial rupture as the cause of haemorrhage and a secondary obstruction of the “corpora fibrosa” in the wall.

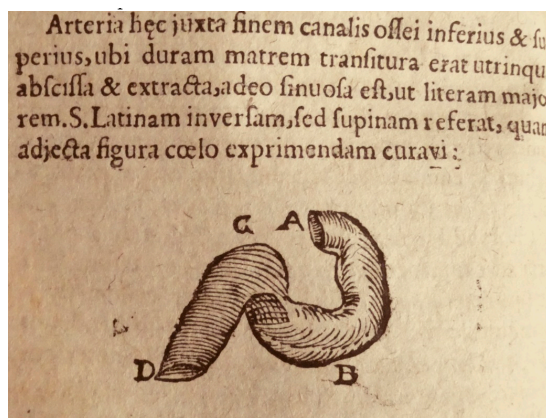


Figure 1. JJ. Wepfer described and drew the carotid siphon. Source: Photo by the author (© Photo by the author from Reference [2]; author books collection).

2. Vascular Origins Identified

In 1677, the iatromathematician François Bayle (1622–1709) in Toulouse first reviewed the various pathophysiological theories of apoplexy, such as brain compression, and then made his own proposition: Calcifications in the carotid walls explain their fragility and their propensity to break or be blocked [3]. In 1684, the English physician and anatomist Thomas Willis (1622–1675) confirmed that, with some exceptions, apoplexy was caused by an intracranial extravasation of blood. For him, the seat of apoplexy was the “callous body,” by which he meant the white matter of the cerebrum [4]. He maintained that the extensive anastomoses between the large cerebral blood vessels (i.e., the circle of Willis) precluded apoplexy that was due to the obstruction of a single artery, but he did not comment on the occlusion of the smaller branches of cephalic arteries [5]. In Pisa, Domenico Mistichelli (1675–1715) demonstrated in 1709 that the side of the body contralateral to the cerebral localisation of the haemorrhage was paralysed [6].

The founding pathological anatomy work by Giovanni Battista Morgagni (1682–1771) owes much to the seventy cases of apoplexy autopsied by Théophile Bonet (1620–1689) in Geneva [7]. Bonet suggested that blood disorders (“thin” or “acid” blood) may favour the extravasation of blood from the vessels. Morgagni did not offer any new concepts, but he did suggest a classification that the Scottish William Cullen (1710–1790) took up again in 1769: sanguine, serous, traumatic, mental, atrabillious, and hydrocephalous apoplexy. The last form, described in children, brings tuberculous meningitis to mind [8]. This classification spread rapidly despite the difficulty of distinguishing between the different forms at the patient’s bedside, as noted in France by Pierre Dan Delavauterie (1780–1868) in his 1807 thesis [9] and by Antoine Portal (1742–1832) in 1811 [10]. Furthermore, while the link between arterial disease and apoplexy was well established, notably by the Scottish anatomopathologist Matthew Baillie (1761–1823) [11], the origin of the serous form remained hypothetical. In 1820, John Cooke (1756–1838) considered serous apoplexy to be rare [12].

3. A Single Cause of Apoplexy, Haemorrhage

As early as 1812 in France, Jean-André Rochoux (1787–1852) [13] only recognised a single cause of apoplexy, haemorrhage, in his thesis: “It essentially consists of haemorrhage by rupture, more or less considerable, sometimes outside the brain but usually within its substance” [14].

The same year, John Cheyne (1777–1836) introduced the concept of cerebral anaemia, i.e., a reduction in cerebral flow. He did not, however, give a clear cause. In those who survived “a stroke of apoplexy,” Cheyne observed a cavity filled with serous fluid in the cerebral matter after their death, indicating resorption in the blood [15]. To this inadvertent description of cerebral infarct, he added the observation of a breathing pattern characterised by alternating periods of apnoea and hyperpnoea, leading to the eponym “Cheyne–Stokes respiration” [16].

4. Cerebral Softening is More Prevalent Than Haemorrhage

In two successive works, in 1820 [17] and then in 1823, Léon Rostan (1790–1866) was the first to attempt to distinguish what he called the cerebral softening of apoplexy, that is, haemorrhagic infarct. According to Rostan, softening was the most frequent cause of hemiplegia, whereas haemorrhage was rare, but he did not fail to mention that haemorrhage may follow softening. He established this new paradigm by comparing it to gangrene in the limbs of the elderly: “The arteries of the brain are usually ossified when this organ is softened”. Softening was thus a well-defined anatomopathological entity that became a disease of the vessels [18]: “The vessels that bring blood and life to the affected organ are ossified not following inflammation but by the ageing process”.

5. Arterial Obstruction as the Pathogenesis

In 1824, François-Claude Lallemand (1790–1853) only saw softening “as partial inflammation of the brain” [19], which Gabriel Andral (1797–1876) was quick to contradict in 1829 [20]. Andral was of Rostan’s opinion that there was a similarity with gangrene in the limbs secondary to “suspension of the circulation by arterial disease”. Baillie, in the last edition of his pathological anatomy treatise in 1818 [21], had already referred to this pathophysiology.

In 1828, John Abercrombie (1780–1844) classified apoplexy into three types depending on the sudden or progressive onset, with or without coma, and with or without functional recovery. He discussed aetiologies involving either arterial spasm blocking circulation or rupture of the arterial wall. He also noted frequent calcifications in the elderly [22]. After being a proponent of the inflammatory theory developed by Lallemand, he became a proponent of Rostan after reading his book. Arterial obstruction as the pathogenesis of softening was controversial for another quarter of a century. For example, the Scottish pathologist Robert Carswell (1793–1857) subscribed to it in 1833 [23], whereas in 1843 [24], the French Maxime Durand-Fardel (1815–1899), following in the footsteps of Jean-Baptiste Bouillaud (1796–1881), maintained that inflammation played a preponderant role [25]. At the same time, Carl Rokitansky (1804–1878) in Vienna drew attention to the frequent association between hypertrophy of the left heart ventricle and apoplexy, indirectly linking arterial hypertension and cerebral haemorrhage [26].

6. Thrombosis and Embolism

In 1847, Rudolf Virchow (1821–1902) made decisive arguments confirming the vascular theory of softening by introducing the concepts of thrombosis and embolism: “These clots never originate in the local circulation but are torn off at a distance and carried along in the blood stream as far as they can go” [27]. In fact, Virchow brought back the notions of clots and arteriosclerosis already proposed (but without garnering much attention) by Jean-Frédéric Lobstein (1777–1835) in Strasbourg in 1829 [28]. In 1852, William Senhouse Kirkes (1822–1864) was the first to describe

three cases of cerebral embolism after finding either clots in the right atrium or valve vegetations [29]. In his thesis defended on 07 March 1862 [30], Étienne Lancereaux (1829–1910) provided a lengthy bibliography of European authors confirming the thromboembolic theory of brain softening.

In 1866, Jean-Baptiste-Vincent Laborde (1830–1903), a student of Rostan, used a microscope to show that softening is a non-inflammatory, organic phenomenon, secondary to damage of the capillary walls in brain tissue and calcareous incrustations. In another attempt in 1866, Adrien Proust (1834–1903) suggested that softening indicated a functional defect of the circle of Willis by the obstruction of backup circulatory routes [31].

7. Experimental Demonstration

Ferdinand Cohn (1828–1898), who became a pioneer in bacteriology, reported numerous experiments in the treatise of von Rokitansky that were conducted in animals involving ligation or injection of inert bodies to block arteries and observe the cerebral lesions downstream [32]. In 1866, Jules Cotard (1840–1889), a student of Jean-Martin Charcot (1825–1893), and Jean-Louis Prévost (1838–1927), a student of Alfred Vulpian (1826–1887), repeated these experiments on rabbits and confirmed that the injection of fine powder (lycopodium spores) or coarser substances (tobacco seeds) triggered different forms of paralysis that varied according to the size of the occlusion and depending on whether it was proximal or peripheral. Tobacco seeds blocked the middle cerebral artery and caused a non-haemorrhagic pinkish softening, comparable to the softening found during the autopsies of their patients. They described the changes over time in the lesions, first involving “anaemic” signs and later infiltrations of blood (hyperaemia) [33].

8. Charcot, Duret, and Foix Lay the Foundations of Current Vascular Neurology

The same year, Charcot recorded the observation of a hemiplegic patient. He proposed a complete explanation of the pathophysiology of cerebral infarction and described the ulceration of an atheromatous plaque at the intima of an artery, on which a clot aggregates, blocks the vessel, or flows downstream as an embolus, causing cerebral ischaemia and parenchymal lesions (Figure 2). Using the term “cholestérine” (cholesterin), the name of cholesterol at the time, he identified the biological nature of atheromatous plaques and made detailed drawings [34].

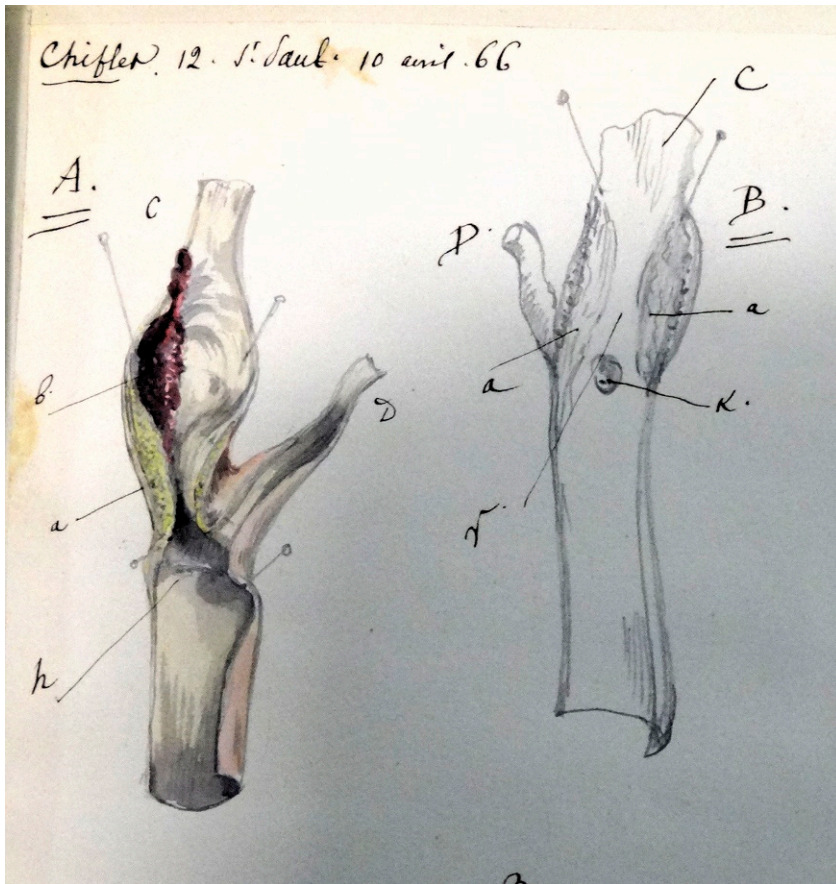
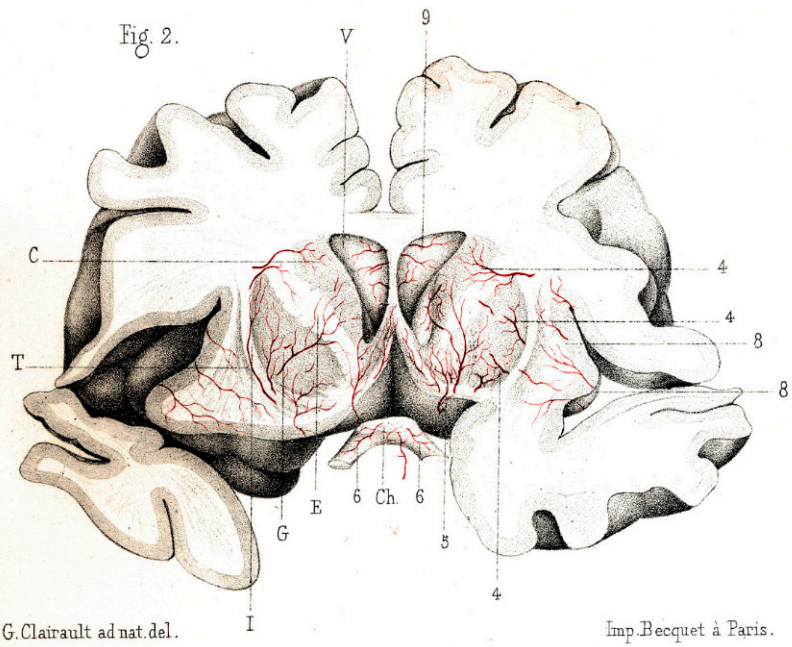
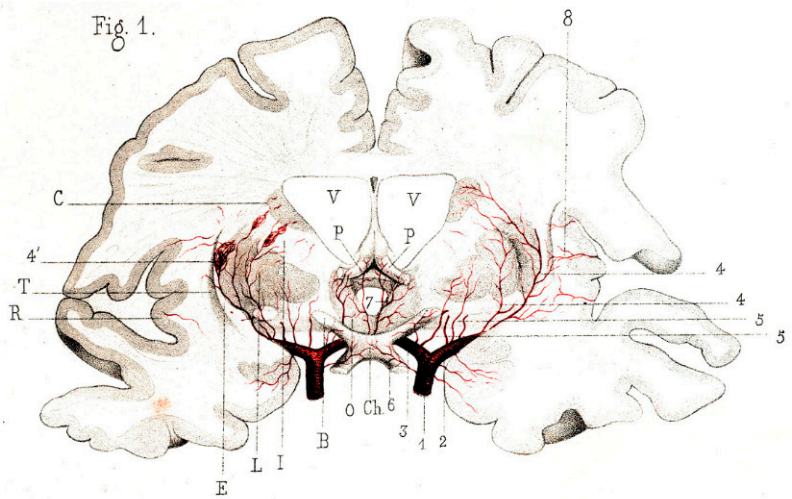


Figure 2. Drawing by Charcot of the ulceration of an atheromatous plaque of the carotide. Bibliothèque Charcot (Source: © Photo by the author; Charcot Library, Sorbonne Université, used with permission).

The decisive step occurred in Charcot's laboratory in 1874. Henri Duret (1849–1921), using injections of coloured gelatine, described the distribution of “supply arteries” of the brainstem, then the cortex, correlating the irrigated territories, infarcted areas, and secondary neurological deficits (Figure 3) [35,36]. Julius Cohnheim (1839–1884) had already proposed this pathophysiology in humans in 1872, more theoretically, and introduced the concept of ischaemic necrosis which he distinguished from haemorrhagic infarct [37].



G. Clairault ad nat. del.

Imp. Becquet à Paris.

G. Masson, Editeur à Paris.

Figure 3. Drawing by Duret the distribution of the basal ganglia's arteries. (Source: Photo by the author from Ref [35]; Author books collection).

Finally, Charles Foix (1882–1927) [38], the first real vascular neurologist, described the clinical syndromes involving each sylvian [39] and basilar [40] arterial territory between 1923 and his death in 1927, ushering in the contemporary era of vascular pathology.

Funding: This research received no external funding.

Acknowledgments: Many thanks to Julien Bogousslavsky, Jacques Poirier and Hubert Déchy for their proofreading and to Anna Fitzgerald for her translation.

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Helian, H. *Dictionnaire du Diagnostic ou l'art de Connoître les Maladies et les Distinguer Exactement les unes des Autres*; Chez Vincent: Paris, France, 1721.
2. Wepfer, J.J. *Observationes Anatomicae, ex Cadaveribus Eorum, quos Sustulit Apoplexia, cum Exercitatione de eius Loco Affecto*; Joh Caspari Suteri: Schaffhausen, Switzerland, 1658.
3. Bayle, F. *Tractatus de Apoplexia: In Quo Hujus Affectionis Causa Penitus Inquiritur & Curatio Exponitur Ex Doctrina Hippocratis*; Guillemette, B.: Tolosæ, France, 1677.
4. Willis, T. *Dr Willis's Practice of Physick, Being the Whole Works of That Renowned and Famous Physician: Containing These Eleven Several Treatises. Two Discourses Concerning the Soul of Brutes. Wherein Most of the Diseases Belonging to the Body of Man Are Treated of, with Excellent Methods and Receipts for the Cure of the Same*; Dring, T.; Harper, C.; Leigh, J.: London, UK, 1684.
5. Tatu, L.; Moulin, T.; Monnier, G. The discovery of encephalic arteries. From Johann Jacob Wepfer to Charles Foix. *Cerebrovasc. Dis.* **2005**, *20*, 427–432. [CrossRef] [PubMed]
6. Finger, S. *Origins of Neuroscience: A History of Explorations into Brain Function*. Oxford University Press: New York, USA, 1994.
7. Schutta, H.S.; Howe, H.M. Seventeenth century concepts of “apoplexy” as reflected in Bonet’s “Sepulchretum”. *J. Hist. Neurosci.* **2006**, *15*, 250–268. [CrossRef]
8. Cullen, W. *Synopsis nosologiae methodicae in usum studiosorum. Editio altera. In Quarta Parte Emendata et Adjectis Morborum Specierus Aucta*; Kincaid A., Creech, W.; Johnston, W.; Cadell, T.; Murray, J.; Dilly, E.: Edinburgi, UK, 1772.
9. Dan Delavauterie, P. *Dissertation sur L'apoplexie Considérée Spécialement Comme l'effet d'une Phlegmasie de la Substance Cérébrale*; Thèse n°68, impr.; Didot Jeune: Paris, France, 1807.
10. Portal, A. *Observations sur la nature et le Traitement de L'apoplexie et sur les Moyens de la Prévenir*; Chez Crochard: Paris, France, 1811.
11. Baillie, M. *The Morbid Anatomy of Some of the Most Important Parts of the Human Body*; Johnson J.: London, UK, 1793.
12. Cooke, J. On Apoplexy including Apoplexia hydrocephalica. In *Treatise on Nervous Diseases*; Cooke, J., Ed.; Longman, Hurst, Rees, Orme, Brown: London, UK, 1820.
13. Walusinski, O. Jean-André Rochoux (1787–1852), a physician philosopher at the dawn of vascular neurology. *Rev. Neurol (Paris)*. **2017**, *173*, 532–541. [CrossRef] [PubMed]
14. Rochoux, J.A. *Propositions sur L'apoplexie*; Thèse n°73, impr.; Didot Jeune: Paris, France, 1812.

15. Cheyne, J. *Cases of Apoplexy and Lethargy with Observations Upon the Comatose Diseases*; Thomas Underwood: London, UK; Adam Black: Edinburgh, UK; Walter Duncan: Glasgow, UK; Gilbert & Hodges: Dublin, Ireland, 1812.
16. Cheyne, J. A case of apoplexy in which the fleshy part of the heart was converted into fat. *Dublin Hosp. Rep.* **1818**, 2, 216–223.
17. Rostan, L. *Recherches sur une Maladie encore peu Connue qui a reçu le nom de Ramollissement du Cerveau*; Béchet et Crevot: Paris, France, 1820.
18. Poirier, J.; Desrouesné, C. La neurologie à l'assistance publique et en particulier à La Salpêtrière avant Charcot, l'exemple de Rostan et du ramollissement cérébral. *Rev. Neurol (Paris)* **2000**, 156, 607–615. [PubMed]
19. Lallemand, F.C. *Recherches Anatomopathologiques sur L'encéphale et ses Dépendances*; Béchet Jeune: Paris, France, 1824–1830.
20. Andral, G. *Précis D'anatomie-Pathologique*; Gabon: Paris, France, 1829.
21. Baillie, M. *The Morbid Anatomy of Some the Most Important Parts of the Human Body*; Nicol, J, &W.: London, UK, 1818.
22. Abercrombie, J. *Pathological and Practical Researches on Diseases of the Brain and the Spinal Cord*; Waugh and Innes: Edinburgh, UK, 1828.
23. Carswell, R. Softening. In *The Cyclopædia of Practical Medicine: Comprising Treatises on the Nature and Treatment of Diseases, Materia Medica and Therapeutics, Medical Jurisprudence, etc.*; Forbes, J., Ed.; Lea & Blanchard: Philadelphia, PA, USA, 1833–1835.
24. Durand-Fardel, M. *Traité du Ramollissement du Cerveau*; Baillière, J.-B.: Paris, France, 1843.
25. Bouillaud, J.B. *Traité Clinique et Physiologique de L'encéphalite ou Inflammation du Cerveau et de Ses Suites: Telles que le Ramollissement, la Suppuration, les Abscesses, les Tubercules, le Squirre, le Cancer, etc.*; Baillière, J.-B.: Paris, France, 1825.
26. Rokitsky von, K. *Handbuch der Speciellen Pathologischen Anatomie*; Braumüller & Seidel: Wien, Austria, 1842.
27. Virchow, R. Über die akute Entzündung der Artérien. *Arch. Für Pathol. Anat. Und Physiol. Und Für Klin. Med. (Virchow Arch.)* **1847**, 1, 272–378. [CrossRef]
28. Lobstein, J.F. *Traité D'anatomie Pathologique*; Chez Levrault F.G.: Paris et Strasbourg, France, 1829.
29. Kirkes, W.S. Detachment of fibrinous deposits from the interior of the heart, and their mixture with the circulating blood. *Med.-Chir. Trans. Lond.* **1852**, 35, 281–324. [CrossRef] [PubMed]
30. Lancereaux, E. *De la Thrombose et de L'embolie Cérébrales Considérées Principalement Dans Leurs Rapports avec le Ramollissement du Cerveau*; Thèse n°39, impr.; Rignoux: Paris, France, 1862.
31. Proust, A. *Des Différentes formes de Ramollissement du Cerveau*; Asselin: Paris, France, 1866.
32. Rokitsky von, K. *Handbuch der Pathologischen Anatomie*; Braumüller & Seidel: Wien, Austria, 1855–1861.
33. Prévost, J.L.; Cotard, J. Études physiologiques et pathologiques sur le ramollissement cérébral. *Comptes Rendus Des Séances Et Mémoires De La Société De Biol.* **1866**, 2, 49–53.
34. Walusinski, O. Charcot and Cholesterin. *Eur. Neurol* **2019**, 81, 309–318. [CrossRef] [PubMed]

35. Duret, H. Recherches anatomiques sur la circulation de l'encéphale. *Arch. De Physiol. Norm. Et Pathol.* **1874**, *6*, 60–91.
36. Walusinski, O.; Courrivaud, P. Henry Duret (1849–1921): A surgeon and forgotten neurologist. *Eur. Neurol* **2014**, *72*, 193–202. [CrossRef] [PubMed]
37. Cohnheim, J. *Untersuchungen Über die Embolischen Prozesse*; Hirschwald: Berlin, Germany, 1872.
38. Caplan, L.R. Charles Foix, the first modern stroke neurologist. *Stroke* **1990**, *21*, 348–356. [CrossRef] [PubMed]
39. Foix, C.; Levy, M. Les ramollissements sylviens. *Rev. Neurol (Paris)* **1927**, *43*, 1–51.
40. Foix, C.; Masson, A. Le syndrome de l'artère cérébrale postérieure. *La Presse Médicale* **1923**, *32*, 361–365.

© 2023 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).