2 Development of knowledge about cerebrovascular disease

'Our knowledge of disorders of the cerebral circulation and its manifestations is deficient in all aspects' was the opening sentence of the chapter on cerebrovascular diseases in Oppenheim's textbook of neurology at the beginning of the 20th century.[1] More than 90 years later this still holds true, despite the considerable advances that have been made. In fact, the main reason for Oppenheim's lament, the limitations of pathological anatomy, is to some extent still valid. True, our methods of observation nowadays are no longer confined to the dead, as they were then. They have been greatly expanded, first by angiography, then by brain imaging and measurement of cerebral blood flow and metabolism, and most recently by non-invasive methods of vascular imaging such as ultrasound and magnetic resonance angiography. Yet, our observations are still mostly anatomical, and after the event. It is only in rare instances that are we able to reconstruct the dynamics of a stroke. At least in haemorrhagic stroke, brain computed tomography (CT) or magnetic resonance imaging (MRI) in the acute phase gives an approximate indication of where a blood vessel has ruptured (though not why exactly there and then) and how far the extravasated blood has invaded the brain parenchyma or the subarachnoid space. With ischaemic stroke, the growth of our understanding has been slower. The ubiquity of the term 'cerebral thrombosis' up to the 1970s exemplifies how deficient our understanding was even at that time.[2] Embolic occlusion, now known to result more often from arterial lesions than from the heart, can be detected in an early phase by non-invasive angiographic techniques or inferred by means of perfusion imaging, but so often the source of the clot is still elusive. We have also learned to distinguish many causes of cerebral infarction other than atherothrombosis, such as arterial dissection, mitochondrial cytopathies and moyamoya syndrome, but the precise pathogenesis of these conditions is still poorly understood.

So it is with humility, rather than in triumph, that we look back on the past. In each era the problems of stroke have been approached by the best minds, with the best tools available. Of course many ideas in the past were wrong, and so presumably are many of our own. Even though we are firm believers in evidence-based medicine, some – perhaps many or even most – of our own notions will not survive the test of time. Our knowledge may have vastly increased in the recent past but it is still a mere island in an ocean of ignorance.

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2.1 Ideas change slowly

The history of medicine, like that of kings and queens in world history, is usually described by a string of dates

and names, by which we leapfrog from one discovery to another. The interval between such identifiable advances is measured in centuries when we describe the art of medicine at the beginning of civilization, but in mere years where our present times are chronicled. This leads to the impression that we are witnessing a dazzling explosion of knowledge. Some qualification of this view is needed, however. First of all, any generation of mankind takes a myopic view of history in that the importance of recent developments is overestimated. The Swedish Academy of Sciences therefore often waits for years, sometimes even decades, before awarding Nobel prizes, until scientific discoveries have withstood the test of time. When exceptions were made for the prize in medicine, the early accolades were not always borne out: Wagner-Jauregg's malaria treatment for neurosyphilis (1927) is no longer regarded as a landmark, while Moniz's prize (1949) for prefrontal leucotomy no longer seems justified; at least he also introduced contrast angiography of the brain, although this procedure may again not survive beyond the end of this century. We can only hope that the introduction of X-ray CT by Hounsfield (Nobel prize for medicine in 1979) will be judged equally momentous by future generations as by ourselves.

Another important caveat if one looks back on progress in medicine is that most discoveries gain ground only slowly. Even if new insights were quickly accepted by peer scientists, which was often not the case, it could still be decades before these had trickled down to the rank and file of medical practitioners. The mention of a certain date for a discovery may create the false impression that this change in medical thinking occurred almost overnight, like the introduction of the single European currency. In most instances, this was far from the truth. An apt example is the extremely slow rate at which the concept of lacunar infarction became accepted by the medical community, despite its potentially profound implications in terms of pathophysiology, treatment and prognosis. The first pathological descriptions date from around 1840,[3,4] but it took the clinicopathological correlations of C. Miller Fisher (Fig. 2.7) in the 1960s before the neurological community and its textbooks started to take any notice.[5–7] And it was not until new techniques for brain imaging in the 1980s provided instantaneous clinicoanatomical correlations that no practising neurologist could avoid knowing about lacunar infarcts – some 150 years after the first description! It is best to become reconciled to the idea that a slow rate of diffusion of new knowledge is unavoidable. The problem is one of all times. Franciscus Biumi, one of the early pathologists, lamented in 1765: *'Sed difficile est adultis novas opiniones inserere, evellere insitas'* (But it is difficult to insert new opinions in adults and to remove rooted ones).[8] How slowly new ideas were accepted and acted upon, against the background of contemporary knowledge, can often be inferred from textbooks, particularly if written by full-time clinicians rather than by research-minded neurologists. Therefore we shall occasionally quote old textbooks to illustrate the development of thinking about stroke.

A reverse problem is that a new discovery or even a new fashion may be interpreted beyond its proper limits and linger on as a distorted idea for decades. Take the discovery of vitamin B_1 deficiency as the cause of a tropical polyneuropathy almost a century ago; the notion that a neurological condition, considered untreatable almost by definition, could be cured by a simple nutritional supplement made such an impact on the medical community that even in some industrialized countries vitamin B_1 is still widely used as a panacea for almost any neurological symptom.

So broadly speaking there are two kinds of medical history, that of the cutting edge of research and that of the medical profession as a whole. The landmarks are easy to identify only with the hindsight of present knowledge. In reality, new ideas often only gradually dawned on consecutive scientists, instead of the popular notion of a blinding flash of inspiration occurring in a single individual. For this reason, accounts of the history of stroke are not always identical.[9,10] Also many important primary sources are not easy to interpret – not only because they were written in Latin, but also because 'new observations' have sometimes been identified only by later historians, in retrospect, while the authors at the time attached no importance to them.[11]

2.2 The anatomy of the brain and its blood supply

From at least the time of Hippocrates (460–370 BC), the brain was credited with intelligence and thought, and also with movements of the opposite side of the body, through observation of unilateral convulsions after head wounds on the contralateral side.[12] Yet, stroke, or 'apoplexy' (Greek for 'being struck down'), was defined as a sudden but mostly general, rather than focal, disorder of the brain. The pathogenesis was explained according to the humoral theory, which assumed a delicate balance between the four humours: blood, phlegm, black bile and yellow bile. Anatomy played almost no part in these explanations. Apoplexy was often attributed to accumulation of black bile in the arteries of the brain, obstructing the passage of animated spirits from the ventricles.[13] Galenus of Pergamon (131–201), a prolific writer and animal experimenter whose

views dominated medicine up to the 17th century,[14] distinguished 'karos' from 'apoplexy', in that respiration was unaffected in the former condition.[15] Leading Islamic physicians like Avicenna (980–1037) tried to reconcile Galenic tenets with the Aristotelian view of the heart as the seat of the mind.[16] In Western Europe, mostly deprived of Greek learning until the fall of Constantinople in 1453 prompted the Renaissance,[17] these Arabic texts were translated into Latin before those of Galen and Hippocrates.[18] All these theories had no anatomical counterpart; dissection of the human body was precluded by its divine connotations. Any illustrations of the human brain that are known before the 16th century are crude and schematic representations of Galenic theories, rather than attempts at copying the forms of nature. As a consequence, many non-neurological disease conditions with sudden onset must have been misclassified as 'apoplexy'.

In 1543 Andries van Wesele (1514–1564), the great Renaissance anatomist who Latinized his name to Andreas Vesalius, produced the first accurate drawings of the brain in his famous book *De humani corporis fabrica libri septem*, with the help of the draughtsman Johan Stephaan van Calcar and the printer Oporinus in Basle.[19] It was the same year in which Copernicus published *De revolutionibus*, proclaiming the sun and not the earth as the centre of the universe.[20] Vesalius largely ignored the blood vessels of the brain, although he retracted an earlier drawing (Fig. 2.1) depicting a '*rete mirabile*', a network of blood vessels at the base of the brain that

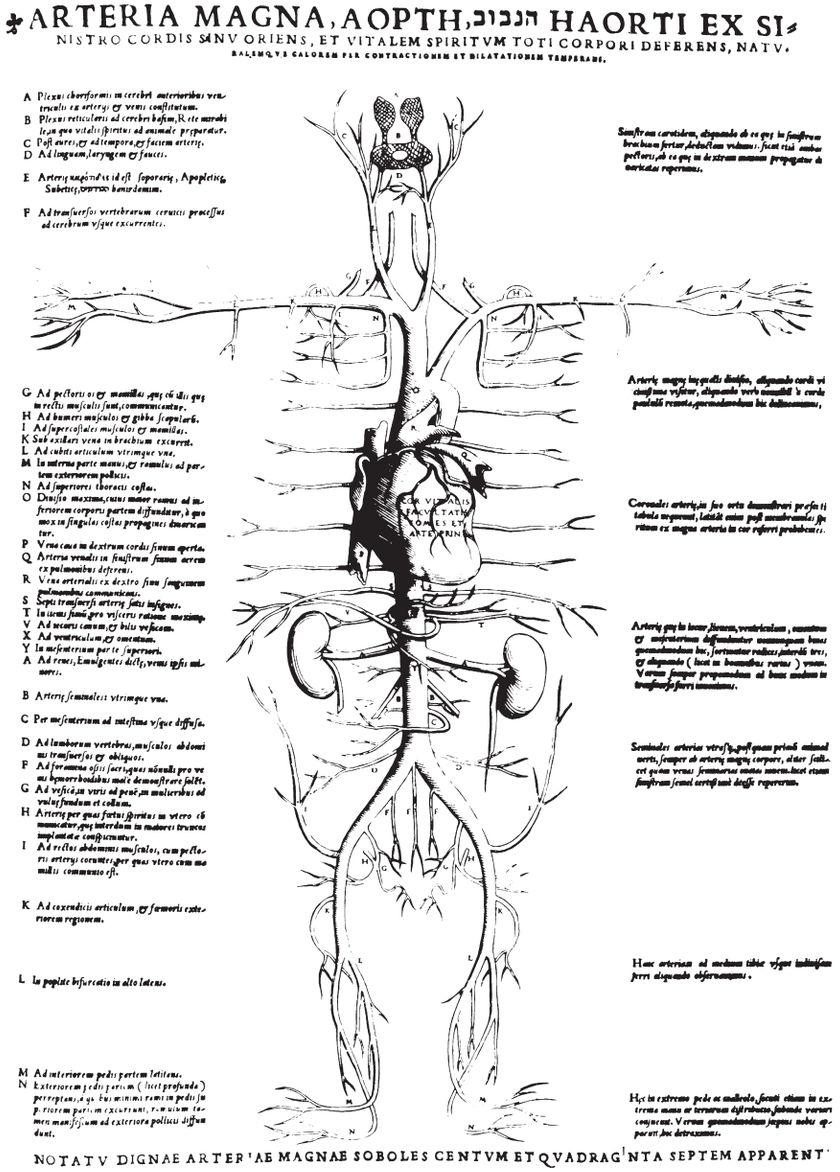

Fig. 2.1 Plate depicting the blood vessels, from Vesalius's *Tabulae Anatomicae Sex*, of 1538.[21] This shows the carotid arteries ending up in a network (b) at the base of the brain; the structures marked (a) represent the choroid plexus in the lateral ventricles. The network of blood vessels (*rete mirabile*) is found in oxen; Galen had assumed it was found also in the human brain, a belief perpetuated throughout the Dark and Middle Ages, up to the early Renaissance. Leonardo da Vinci had also drawn a (human?) brain with a '*rete mirabile*' at its base.[22] Vesalius retracted the existence of a network in his atlas of 1543.

Galen had found in pigs and oxen and that had been extrapolated to the human brain ever since.[21,22] Before him, Berengario da Carpi had also denied the existence of the *rete*.[23] Vesalius was vehemently attacked by traditionally minded contemporaries as an iconoclast of Galenic dogmas. Nevertheless, initially, he did not go as far as outright opposition to the central Galenic tenet that blood could pass through the septum between the right and left ventricle of the heart, allowing the mixture of blood and air and the elimination of 'soot'. Instead, he praised the creator for having made the openings so small that nobody could detect them, another striking example of how the power of theory may mislead even the most inquisitive minds. Only later, in the 1555 edition of his *De humani corporis fabrica*, did he firmly state that the interventricular septum was tightly closed. The decisive blow to the humoral theory came in 1628, through the description of the circulation by William Harvey (1578–1657);[24] it need no longer surprise us that it took many decades before these views were widely accepted. Harvey's work formed the foundation for the recognition of the role of blood vessels in the pathogenesis of stroke.

Thomas Willis (1641–1675) is remembered not so much for having coined the term 'neurology', or for his iatrochemical theories, a modernized version of humoral medicine, or for his part in the successful resuscitation of Ann Green after judicial hanging,[25] as he is for his work on the anatomy of the brain, first published in 1664,[26] especially for his description of the vascular interconnections at the base of the brain (Fig. 2.2).[27] Before him, Fallopius, Casserio, Vesling and Wepfer had all observed at least part of the circle,[28–31] in the case of Casserio and Vesling even with an illustration.[32] But undisputedly, it was Willis who grasped the functional implications of these anastomoses in a passage illustrating his proficiency in performing necropsies as well as postmortem experiments (from a posthumous translation):[33]

> We have elsewhere shewed, that the *Cephalick* Arteries, viz. the *Carotides*, and the *Vertebrals*, do so communicate with one another, and all of them in different places, are so ingraffed one in another mutually, that if it happen, that many of them should be stopped or pressed together at once, yet the blood being admitted to the Head, by the passage of one Artery only, either the *Carotid* or the *Vertebral*, it would presently pass thorow all those parts exterior and interior: which indeed we have sufficiently proved by an experiment, for that Ink being squirted in the trunk of one Vessel, quickly filled all the sanguiferous passages, and every where stained the Brain it self. I once opened the dead Carcase of one wasted away, in which the right Arteries, both the *Carotid* and the *Vertebral*, within the Skull, were become bony and impervious, and did shut forth the blood from that side, notwithstanding the sick person was not troubled with the astonishing Disease.

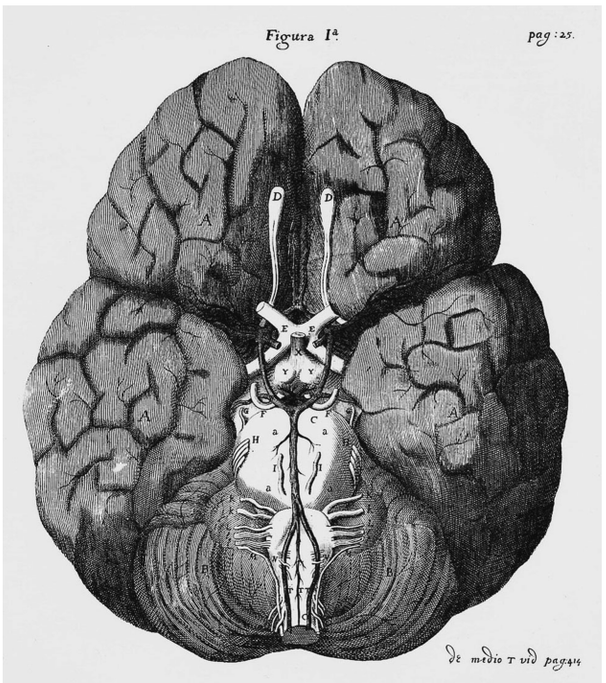

Fig. 2.2 Illustration of the base of the brain from Willis's *Cerebri Anatome* (1664),[26] showing the interconnections between the right and left carotid systems, and also between these two and the posterior circulation (drawing by Christopher Wren).

It seems that the idea of infusing coloured liquids into blood vessels, practised from 1659 onwards and later perfected by Frederik Ruysch (1638–1731) and in the next century by John Hunter (1728–1793),[34,35] had come from Christopher Wren (1632–1723).[25] Wren also made the etchings for Willis's book (he is now mainly remembered as the architect of St Paul's Cathedral and many other churches built after the great fire of London in 1666).

2.3 What happens in 'apoplexy'?

Willis's 'astonishing Disease', apoplexy, had of old intuitively been attributed to some ill-defined obstruction, whether from want of 'animal spirits' via the nerves in

the tradition of Greek medicine, or, after Harvey's time, by deprivation of blood flow. Yet, it should be remembered that the notion of an intrinsic 'nervous energy' only slowly lost ground. Even the great 18th-century physician Boerhaave, though clearly recognizing the role of blood vessels and the heart in the development of apoplexy, invoked obstruction of the cerebrospinal fluid.[36] In Table 2.1 we have provided a schematic representation of the development of ideas about apoplexy through the ages, together with its relationship to arterial lesions. That Willis had found 'bony' and 'impervious' arteries in patients who actually had not died from a stroke was probably the reason that he was not outspoken on the pathogenesis of apoplexy. His contemporaries, Wepfer (1620–1695) in Schaffhausen, and Bayle (1622–1709) in Toulouse, only tentatively associated apoplexy with 'corpora fibrosa',[31] or with calcification of cerebral arteries.[37]

Wepfer (Fig. 2.3) not only recognized arterial lesions, but he also prompted one of the great advances in the knowledge about stroke by distinguishing between, on the one hand, arterial obstruction preventing the influx of blood and, on the other, extravasation of blood into the substance of the brain or the ventricular cavities. His interpretation was, however, that blockage of arteries as well as extravasation of blood impeded the transmission of 'spiritus animalis' to the brain.[11] Accordingly, he regarded apoplexy as a process of global stunning of the brain, while the focal nature of the disease largely escaped him. The four cases of haemorrhage Wepfer described were massive, at the base of the brain or deep in the parenchyma. In cases with obvious hemiplegia, incidentally a term dating back to the Byzantine physician Paulus Aegineta (625–690),[38] Wepfer suspected dysfunction of the ipsilateral rather than the contralateral side. He also observed patients who had recovered from apoplectic attacks, and noted that those most liable to apoplexy were 'the obese, those whose face and hands are livid, and those whose pulse is constantly unequal'.

That the paralysis was on the opposite side of the apoplectic lesion was clearly predicted by Domenico Mistichelli (1675–1715) from Pisa on the basis of his observation of the decussation of the pyramids (Fig. 2.4).[39] A landmark in the recognition of the anatomical substrate of stroke – and of many other diseases – was the work of Morgagni (1682–1771), professor of medicine and subsequently of pathological anatomy in Padua. In 1761 Morgagni published an impressive series of clinicopathological observations collected over a lifetime (he

Fig. 2.3 Johann Jakob Wepfer (1620–1695).

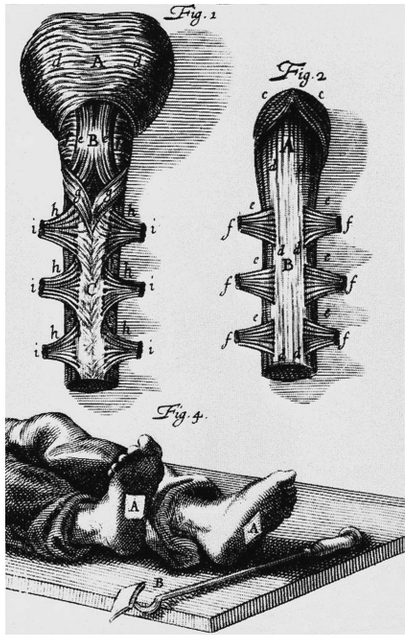

Fig. 2.4 Illustration from Mistichelli's book on apoplexy (1709) in which he shows the decussation of the pyramids and also the outward rotation of the leg on the paralysed side.[39]

Table 2.1 Development of ideas about 'apoplexy' and its relationship with arterial lesions.

Medical scientist	Ideas about 'apoplexy'				
	Haemorrhagic	Non-haemorrhagic	Medical scientist	Observations on arterial lesions	Historical events
Hippocrates (Kos) (460–370 BC)[13]	Sudden loss of consciousness, as a result of brain disease				
Galenus (Pergamum and Rome) (131–201)[15]	Sudden loss of consciousness, as a result of brain disease				0 Birth of Jesus Christ
Wepfer (Schaffhausen) (1620–1695)[31]	Extravasation of blood in brain tissue (1658)		Wepfer (1658)	'Corpora fibrosa'	1642 Rembrandt paints *Night Watch*
			Bayle (Toulouse) (1622–1709)[37]	Calcifications (1677)	1682 Peter I ascends Russian throne
Mistichelli (Pisa) (1675–1715)[39]	Paralysis is unilateral, and crossed with respect to lesion (1709)		Willis (Oxford) (1621–1675)[33]	'Bony, impervious arteries' (1684)	1707 Union between England and Scotland
Boerhaave (Leiden) (1668–1738)[36]	'Stoppage of the spirits'		Boerhaave	Narrowing due to cartilaginous change (1735)	1729 Bach writes *St Matthew Passion*
Morgagni (Padua) (1682–1771)[40]	'Sanguineous apoplexy' (1761)	'Serous apoplexy', extravasation of serum? (1761)	Baillie (London) (1761–1823)[42]	Hardening of arteries associated with haemorrhage? (1795)	1776 US Declaration of Independence
Rostan (Paris) (1790–1866)[57]		'Ramollissement' (1820): – softening more frequent than haemorrhage – condition not inflammatory?	Rostan	Ossification of cerebral arteries (1820)	1815 Battle of Waterloo; Schubert writes *Erlkönig*

Lallemand (Montpelier) (1790–1853)[58]	Cerebral softening is definitely inflammatory in nature (1824)	Lobstein (Strasbourg) (1777–1835)[67]	'Arteriosclerosis' (1829)	1829 Stephenson builds the railway engine called 'The Rocket'
Abercrombie (Edinburgh) (1780–1844)[60]	Cerebral softening analogous to gangrene of limb? (1836)	Abercrombie	Due to ossification of arteries?	1837 Queen Victoria ascends the throne of the British Empire
Carswell (London) (1793–1857)[62]	Cerebral softening caused by obliteration of arteries? (one of possible causes; 1838)			1848 Year of revolutions; Louis Napoleon elected president of France
Rokitansky (Vienna) (1804–1878)[219]	'Encephalomalacia' (1844): – white, or serous (congestion) – red (inflammatory) – yellow (frequent; unexplained)			1859 Darwin publishes *The Origin of Species* 1863 Manet paints *Le Déjeuner sur l'herbe*
Cruveilhier (Paris) (1791–1874)[63]	Cerebral softening caused by capillary congestion, secondary to 'irritation' (1842)	Virchow	Arteriosclerosis leads to thrombosis; thrombi may be torn off and lodge distally ('embolism') (1856)	1869 Opening of the Suez Canal 1871 Stanley meets Livingstone at Ujiji
Virchow (Berlin) (1821–1902)[66]	'Yellow softening' of the brain is secondary to arterial obliteration; any inflammation is secondary (1856)	Cohnheim	End-arteries most vulnerable; paradoxical embolism	1877 Bell invents telephone, Edison the phonograph
Cohnheim (Berlin) (1839–1884)[68]	'Infarction' (stuffing) is haemorrhagic by definition, as opposed to ischaemic necrosis (1872)	Chiari (Prague) (1851–1916)[70]	Thrombosis at the carotid bifurcation may cause secondary embolization to brain (1905)	1895 Röntgen discovers X-rays in Würzburg 1907 Ehrlich introduces arsphenamine as treatment for syphilis

was 79 at the time of publication), in which he firmly put an end to the era of systemic (humoral) theories of disease and replaced them by an organ-based approach, though he did not include even a single illustration; characteristically, the title of the book was *'De sedibus et causis morborum . . .'* (about the sites and causes of disease).[40] Morgagni not only confirmed the notion of crossed paralysis but also firmly divided apoplexy into 'sanguineous apoplexy' and 'serous apoplexy' (and a third form which was neither serous nor sanguineous). A decade later, Portal (1742–1832) rightly emphasized that it was impossible to distinguish between these two forms during life.[41] However, it would be a mistake to assume that 'serous' (non-haemorrhagic) apoplexy was recognized at that time as being the result of impaired blood flow, let alone of mechanical obstruction of blood vessels. Some even linked the arterial hardening with brain haemorrhages and not with the serous apoplexies.[42] Although we quoted 17th-century scientists such as Bayle and Wepfer in that they associated some non-haemorrhagic cases of apoplexy with obstruction of blood flow, in the 18th century medical opinion swayed towards 'vascular congestion', a kind of pre-haemorrhagic state. That explanation was propounded not only by Morgagni[40] but also by many of his contemporaries and followers.[41,43,44] John Cheyne (1777–1836) pointed out that autopsy in patients who had survived a 'stroke of apoplexy' for a considerable time might show a cavity filled with rusty serum that stained the adjacent brain tissue, but he may have been describing a residual lesion after cerebral haemorrhage rather than infarction.[45]

The anatomical, organ-based approach exemplified by Morgagni reflected the Italian practice, in which the separation between physicians and surgeons was much less strict than in northern Europe with its more theoretical framework of medicine. The protagonists of the Northern school of thinking were Herman Boerhaave (1668–1738) in Leiden and later William Cullen (1710–1790) in Edinburgh, the most influential clinical teachers of their time. They established a nosological classification that was based much more on holistic theory, in terms of a disturbed system, than on actual observations at the level of the organ, at least with 20th-century hindsight.[46] Probably our own time will be branded as the era of exaggerated reductionism! In the intellectual tradition of the Dutch-Scottish school, purely clinical classifications of apoplexy were proposed in the early 19th century by Serres (with and without paralysis),[47] by Abercrombie (primary apoplexy, with deprivation of sense and motion, and sometimes with convulsions, a second type beginning with headache, and a third type with loss of power on one side of the body and of speech, often with recovery),[48] and by Hope and Bennett (transient apoplexy, primary apoplexy with death or slow recovery, ingravescent apoplexy with partial recovery and relapse, and paraplexic apoplexy with paralysis).[49]

There are several reasons why the brain lesion in what we now call cerebral infarction was not identified until the middle of the 19th century. First, it was impossible to recognize ischaemic softening in patients who had usually died not long after their stroke. Fixation methods were not available until the end of the 18th century; Vicq d'Azyr, Marie Antoinette's physician, was the first to use alcohol as a tissue fixative,[50] while formaldehyde fixation was not employed until a century later.[51] Second, it is probable that many patients diagnosed as having died from apoplexy in fact had suffered from other conditions. If in our time the diagnosis is wrong in 20–30% of patients referred with a presumed stroke,[52–54] the diagnostic accuracy was presumably no better in centuries past.

2.4 Cerebral infarction (ischaemic stroke)

After Morgagni's seminal book the organ-based approach to medicine quickly spread from Italy to other countries. In France, the first proponents were surgeons. After the French revolution the strict distinction between medicine and surgery disappeared, driven by the reorganization of hospital care (no longer managed by the church but by the state) and by the need to train a large number of new doctors, for military as well as civilian duties ('peu lire, beaucoup voir, beaucoup faire').[55,56] It was Leon Rostan (1790–1866; Fig. 2.5), a physician at the Salpêtrière in Paris, who clearly recognized softening of the brain as a separate lesion, distinct from haemorrhage, although the pathogenesis still escaped him. He published his findings in an unillustrated monograph, the first edition of which appeared in 1820.[57] The lesions were most commonly found in the corpus striatum, thalamus or centrum semiovale, but they also occurred in the cerebral cortex, brainstem and cerebellum. Old cases showed a yellowish-green discoloration, whereas if the patients had died soon after the event the colour of the lesion was chestnut or reddish. The softening might be so extreme as to lead to the formation of a cyst. In other patients it was difficult to detect any change in firmness or in colour. Rostan distinguished softening of the brain from 'apoplexy', a term he no longer used for stroke in general, but which he regarded as being synonymous with haemorrhagic stroke. He supposed that softening of the brain was more common than brain haemorrhage, although some haemorrhages were secondary to softening. The clinical manifestations were thought

Fig. 2.5 Léon Rostan (1790–1866).

to occur in two stages: first 'fugitive' disturbances in the use of a limb, in speech or in visual or auditory perception, sooner or later followed by hemiplegia and coma, in a slowly progressive fashion.

Although Rostan recognized 'ossification' of the cerebral arteries, he did not associate these lesions with cerebral softening via obstruction of the arterial system. At any rate he doubted the prevailing opinion that the primary lesion was some kind of inflammatory response. After all, there was redness and swelling (*rubor*, *tumor*), if not warmth and pain (*calor*, *dolor*), to complete the cardinal signs of inflammation delineated by Celsus in the first century AD. Rostan's contemporary Lallemand (1790–1853) was much more outspoken and had little doubt that inflammation was at the root of cerebral softening.[58] Readers trained in the 21st century may find this difficult to understand but they should be aware that 'inflammation' was a rather common explanation for disease from the middle of the 18th century until some hundred years later.[46] Just as in our time some poorly understood medical conditions are often interpreted in terms of autoimmune disease, perhaps erroneously, inflammation seemed for a long time the most logical 'paradigm' to fall back on to explain liquefaction of brain tissue.[59]

The first inkling of a relationship between arterial disease and 'ramollissement', as many English writers continued to call brain softening in deference to Rostan, was voiced by Abercrombie, in a later edition of his textbook.[60] He drew an analogy with gangrene, caused by 'failure of circulation', this in turn being secondary to 'ossification of arteries'. The role of arterial obstruction as a primary cause of softening of the brain was confirmed by others,[61,62] but the theory of inflammation continued to be defended by a few adherents.[63,64] Some were aware that apoplexy could be caused by 'cerebral anaemia' (as opposed to congestion), not only through loss of blood but also by a reduced vascular pressure, particularly in the case of heart disease.[44]

Other missing links in the understanding of cerebral infarction were clarified by Rokitansky (1804–1878) in Vienna and by Virchow (1821–1902) in Berlin. Rokitansky divided cerebral softening (which he termed encephalomalacia) into three varieties: red (haemorrhagic) softening, inflammatory in nature; white softening (synonymous with 'serous apoplexy') caused by congestion and oedema; and, the most common variety, yellow softening, of which the pathogenesis was unknown.[219] Virchow (Fig. 2.6) revolutionized medical thinking about vascular disease by firmly putting the

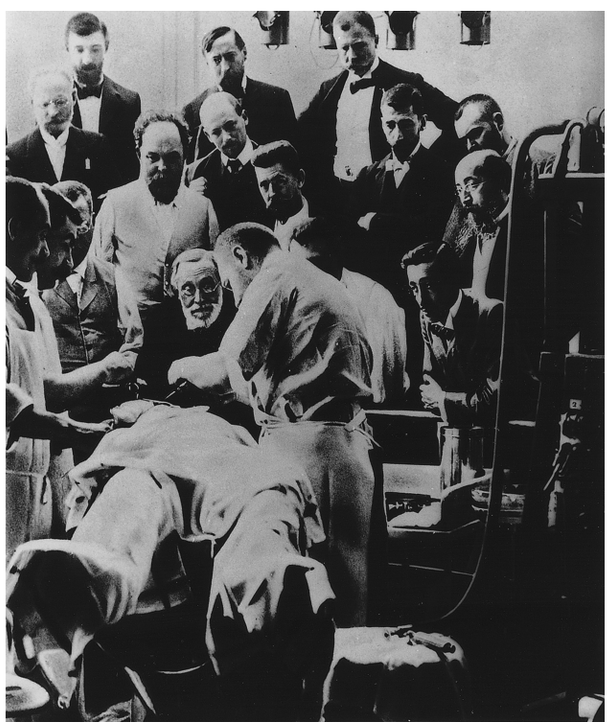

Fig. 2.6 Rudolph Virchow (1821–1902) teaching at a postmortem in the Charité Hospital in Berlin.

emphasis on changes in the vessel wall rather than in blood; Schiller called it the victory of 'solidism' over 'humoralism'.[9] Virchow also firmly established that thrombosis of arteries was caused not by inflammation but by fatty metamorphosis of the vessel wall, even if he had to found his own journal before his papers could be published.[65,66] To describe the changes in the arterial wall Virchow revived the term 'arteriosclerosis', first used by Lobstein.[67] Virchow's disciple Julius Cohnheim coined the culinary term 'infarction' (from the Latin verb *infarcire*, 'to stuff into'), but strictly reserved it for haemorrhagic necrosis ('stuffing', by seeping of blood into ischaemic tissue, through damaged walls of capillaries) as opposed to ischaemic necrosis.[68]

2.5 Thrombosis and embolism

Virchow observed thrombosis as the result of atherosclerosis, and also embolism, in patients with gangrene of the lower limbs caused by clots from the heart. The term 'embolism' was newly coined by him, at least in medical parlance. He extrapolated these events to the cause of cerebral softening:

> Here there is either no essential change in the vessel wall and its surroundings, or this is ostensibly secondary. I feel perfectly justified in claiming that these clots never originated in the local circulation but that they are torn off at a distance and carried along in the blood stream as far as they can go.[65]

The relationship between vegetations on the heart valves and stroke had in fact been suggested a century earlier by Boerhaave's pupil Gerard van Swieten, personal physician to the Austrian empress Maria Theresa and founder of the Viennese school of medicine:

> It has been established by many observations that these polyps occasionally attach themselves as excrescences to the columnae carneae of the heart, and perhaps then separate from it and are propelled, along with the blood, into the pulmonary artery or the aorta, and its branches . . . were they thrown into the carotid or vertebral arteries, could disturb – or if they completely blocked all approach of arterial blood to the brain – utterly abolish the functions of the brain.[69]

For more than a century after Virchow's accurate pathological descriptions of arterial occlusions, the term 'cerebral embolism' was almost synonymous with embolism from the heart (parenthetically, it still is, in many contemporary textbooks and papers – another illustration of how slowly ideas change). Sources of embolism in the extracranial arteries were hardly considered until the 1960s, at least in teaching. By the same token, the term 'cerebral thrombosis' remained firmly entrenched in clinical thinking as being more or less synonymous with cerebral infarction without associated heart disease, the implication being that in these cases the site of the atheromatous occlusion was in the intracranial vessels. For example, this is what the sixth edition of Brain's *Diseases of the Nervous System* says on the subject in 1968:

> Progressive occlusion of cerebral blood vessels impairs the circulation in the regions they supply. The effects of this depend upon the size and situation of the vessel, and the rate of onset of the occlusion particularly in relation to the collateral circulation. Actual obstruction of an artery by atheroma, with or without subsequent thrombosis, causes softening of the region of the brain supplied by the vessel.[2]

That the notion of 'local thrombosis' persisted for such a long time must have been because of its appealing simplicity, not by lack of observations to the contrary. As long ago as 1905, Chiari drew attention to the frequency of atherosclerosis in the region of the carotid bifurcation and suggested that embolization of atheromatous material might be a cause of cerebral softening,[70] and not much later Hunt described the relationship between carotid occlusion and stroke.[71] The much later general acceptance of *extracranial* atherosclerosis as an important cause of cerebral ischaemia was prompted by two further developments. The first was the attention generated by Fisher's studies, in which he re-emphasized the role of atherosclerosis at the carotid bifurcation, at least in white patients.[72] He clinically correlated these lesions not only with contralateral hemiplegia but also with attacks of monocular blindness in the ipsilateral eye.[73] The second development was imaging. Cerebral angiography by direct puncture of the carotid artery had been introduced by Moniz in 1927,[74,75] but imaging of the carotid bifurcation in patients with stroke became common only after the advent of catheter angiography,[76] and later of ultrasound techniques. Now it is modern CT or MR angiography that often shows abnormalities of the internal carotid artery near its origin, at least in patients with transient or permanent deficits in the territory of the main trunk of the middle cerebral artery or one of its branches. The earlier patients are investigated, the greater the chance of detecting the site where the embolus has become impacted in the cerebral arterial tree. The therapeutic implications of identifying lesions in the carotid artery in symptomatic patients became clear through the two large randomized controlled trials of carotid endarterectomy in the 1980s and 1990s,

which showed overall benefit from the operation for severe degrees of stenosis.[77]

In 25–30% of patients with temporary or permanent occlusion of large intracranial vessels no source of embolism can be found in the neck or in the heart.[78,79] Pathological observations suggesting that the aorta may harbour atherosclerotic lesions[80] have been confirmed in a large autopsy series and by transoesophageal echocardiography during life.[81,82] Of course, there is more to ischaemic stroke than embolism from large vessels, but the history of small vessel disease and non-atheromatous causes of ischaemia is rather more recent.

Before concluding the sections on cerebral infarction, thrombosis and embolism, we should like briefly to draw attention to the term 'cerebrovascular accident', which enjoyed some undeserved popularity in the middle half of the last century. The problem was that sometimes the term was used as a synonym for cerebral infarction, at other times to denote stroke in general. In this day and age the term is a highly specific sign of woolly thinking. We can do no better than quote Schiller:[9]

> That rather blurry and pompous piece of nomenclature must have issued from the well-meant tendency to soften the blow to patients and their relatives, also from a desire to replace 'stroke', a pithy term that may sound unscientific and lacking gentility. 'Cerebrovascular accident (CVA)' can be traced to the early 1930s – between 1932, to be exact, when it was still absent from the 15th edition of *Dorland's Medical Dictionary*, and the following edition of 1936 where it first appeared.

The occasional medical student or junior doctor who still takes refuge in the term 'CVA' in an attempt to cover up ignorance about the precise type of cerebrovascular event in a given patient (while avoiding sharing the term 'stroke' with the laity) should either find out or come clean about not knowing.

2.6 Transient ischaemic attacks

It is difficult to trace the first descriptions of what we now call transient ischaemic attacks (TIAs) of the brain or eye, because symptoms representing focal deficits were not clearly distinguished from non-specific symptoms of a more global nature such as fainting or headache.[83] Wepfer recorded that he had seen patients who recovered from hemiplegia in one day or less.[31] An 18th-century account has been retrieved in the patient's own words, not muddled by medical interpretation, which makes it as lucid as it would have been today. The subject is Jean Paul Grandjean de Fouchy, writing in 1783, at the age of 76 years:[84]

> Toward the end of dinner, I felt a little increase of pain above the left eye and in that very instant I became unable to pronounce the words that I wanted. I heard what was said, and I thought of what I ought to reply, but I spoke other words than those which would express my thoughts, or if I began them I did not complete them, and I substituted other words for them. I had nevertheless all movements as freely as usual . . . I saw all objects clearly, I heard distinctly what was being said; and the organs of thought were, it seemed to me, in a natural state. This sort of paroxysm lasted almost a minute.

Once it had become established, in the middle of the 19th century, that cerebral softening was not caused by an inflammatory process but by occlusion of cerebral arteries, temporary episodes of ischaemia were recognized increasingly often in the next few decades.[1,85–89] In the course of time, three main theories have been invoked to explain the pathophysiology of TIAs, at least in relation to atherosclerosis: the vasospasm theory, the haemodynamic theory and the thromboembolic theory.[83]

2.6.1 The vasospasm theory

Arterial spasm as a cause of gangrene of the extremities was described by Raynaud (1834–1881) in his doctoral thesis of 1862.[90] Others extrapolated his theory of vasospasm to the cerebral circulation.[91,92] Russel, writing in 1909 about a 50-year-old farmer who had suffered three attacks of tingling and numbness in the right arm and the right side of the face, dismissed thrombosis ('Thrombus, once formed, does not break up and disappear in some mysterious way') and instead invoked a phenomenon of 'local syncope', analogous to Raynaud's disease or some cases of migraine: 'There must be some vessel constriction, local in site, varying in degree and in extent, coming and going, intermittent'.[92] Even the great Osler mounted the bandwagon of the vasospastic theory to explain transient attacks of aphasia and paralysis: 'We have plenty of evidence that arteries may pass into a state of spasm with obliteration of the lumen and loss of function in the parts supplied'.[89] Vasospasm remained the most popular theory to explain TIAs in the first half of the 20th century and provided the rationale for so-called cerebral vasodilators. Up to the 1980s these useless drugs were still widely prescribed in some European countries, not only for TIAs but for 'senility' in general; in France they were the third most commonly prescribed medication in 1982.[93]

In the front line of medicine, however, the vasospastic theory went into decline soon after World War II, firstly

because the cerebral arteries are among the least reactive in the body,[94,95] and secondly because more plausible theories emerged (see below). Only under strictly defined conditions can vasospasm be a causal factor in the pathogenesis of cerebral ischaemia, that is, after subarachnoid haemorrhage or in association with migraine, and even in these conditions its role is contentious. Nevertheless, vasospasm has resurfaced as a possible cause of episodes of transient monocular blindness that are frequent and stereotyped and have no altitudinal distribution,[96] or even of transient motor or sensory deficits not related to migraine.[97] Such events must be extremely rare.

2.6.2 The haemodynamic theory

The notion of 'low flow' without *acute* vessel obstruction as a cause of cerebral ischaemia should perhaps be attributed to Ramsay Hunt, who drew an analogy between the symptoms of carotid stenosis or occlusion and the symptoms of intermittent claudication in patients with severe peripheral arterial disease.[71] But, it was especially after 1951, when Denny-Brown suggested that TIAs might be caused by 'episodic insufficiency in the circle of Willis',[95] that interest in the haemodynamic aspects of TIAs was fully aroused. Indeed, it was mainly the surgical community for which the concept of 'cerebral intermittent claudication' continued to have great appeal, despite the incongruity of the relatively constant blood flow to the brain and the large fluctuations in flow that occur in the legs, depending on their level of activity.

Clinical studies failed to support the notion of haemodynamic failure. After artificial lowering of the blood pressure by means of hexamethonium and postural tilting, in 35 patients who had either experienced TIAs or who had known carotid artery disease, only one of the patients developed symptoms of focal cerebral ischaemia before a syncopal attack which signified global rather than focal ischaemia of the brain.[98] Similarly, cerebral ischaemia with naturally occurring attacks of hypotension, such as cardiac arrhythmias, is almost always syncopal and not focal in nature,[99] and cardiac arrhythmias do not occur more often in patients with TIAs than in controls.[100] Once the first successful carotid reconstruction had been reported,[101] the intuitive belief in the haemodynamic theory led to an ever-increasing number of carotid endarterectomies being performed (indeed, often called 'carotid disobstruction') in patients with and even without TIAs, despite the absence of any formal proof of efficacy. These developments caused understandable concern in the neurological community.[102,103] Fortunately the controversy prompted well-designed clinical trials, which have served to define to a large extent the role of this operation.[77]

That the haemodynamic theory does not apply to most patients with TIAs is not to say that the exceptional patient cannot suffer from 'misery perfusion'.[104] In the presence of multiple occlusions or stenoses of the extracranial arteries, the haemodynamic reserve may be so poor that minor changes in systolic blood pressure cannot be compensated for. Such triggering events include a change from a sitting to a standing position, turning the head, heating of the face or looking into bright light.[105–107] Perhaps for this small group of patients extracranial-intracranial bypass surgery has something to offer after all, despite the negative results of the randomized trial in a large but relatively unselected group of patients with occlusion of the internal carotid or middle cerebral artery.[108]

2.6.3 The thromboembolic theory

In the 1950s C. Miller Fisher (Fig. 2.7) not only gave new impetus to some older observations about the relationship between stroke and atheromatous lesions of

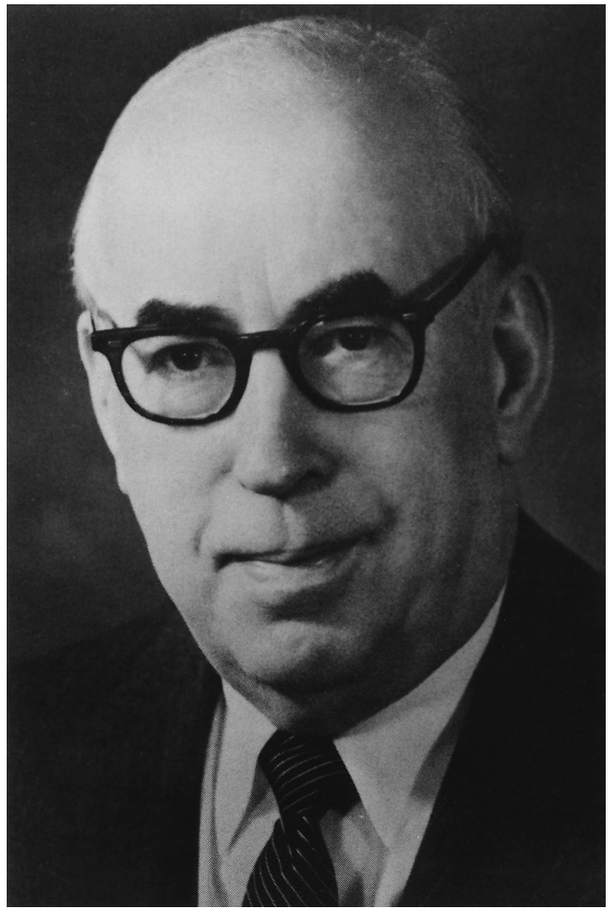

Fig. 2.7 C. Miller Fisher (1913–).

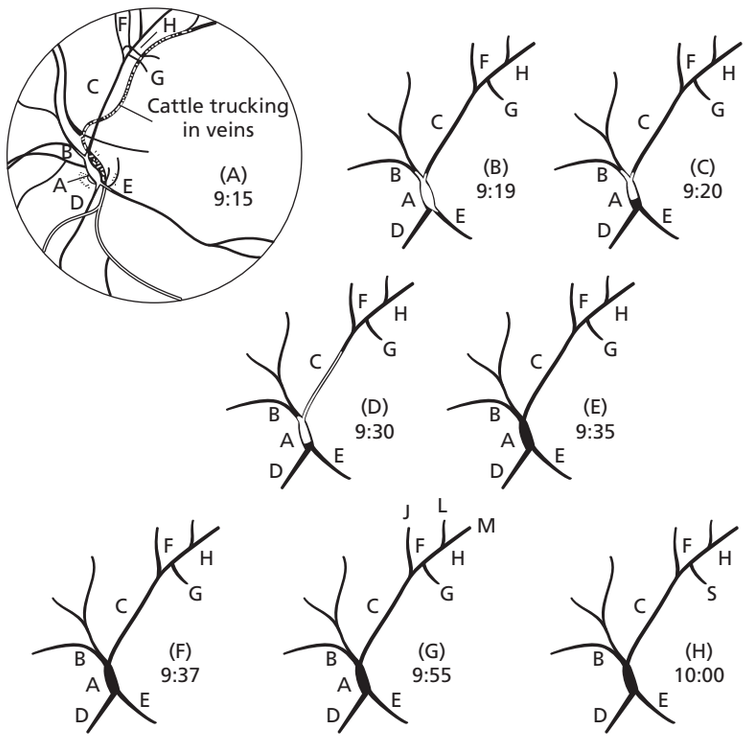

Fig. 2.8 Diagrams of observations in a patient with an attack of transient monocular blindness in the left eye (except the upper temporal quadrant); the attack had started at 8.55 am, 20 minutes before the beginning of the observations. The column of blood in the retinal arteries was in some places interrupted by white segments, initially at the stems of the superior and inferior retinal arteries (A); also the column of blood in at least six venous branches of the superior half of the retina was broken into transverse bands (so-called cattle trucking). The white segments in the retinal arteries slowly passed through the superior temporal artery (B–H). At (C) the vision in the upper half of the visual field had returned. At (D) a fine trickle of erythrocytes moved slowly along one side of white segment AB to the superior nasal artery, and at (E) vision had also returned in the inferior temporal quadrant. After (H), when the column of blood had been completely restored, vision returned to normal. (From Fisher, 1959;[109] by kind permission of the author and *Neurology*.)

the carotid bifurcation, but he also provided evidence that the pathogenesis was more complex than could be explained by fixed arterial narrowing. First, he saw a patient in whom hemiplegia had been preceded by attacks of transient monocular blindness in the contralateral eye, that is, 'the wrong eye'.[73] Second, through assiduous ophthalmoscopic observations, he saw white bodies passing slowly through the retinal arteries during an attack of transient monocular blindness (Fig. 2.8), the whitish appearance and friability of the moving material suggesting that these were emboli, largely made up of platelets.[109] These findings were confirmed by Ross Russell,[110] whilst others saw atheromatous emboli in the retinal vessels, which did not move but had become impacted.[111,112]

After these direct observations of the ocular fundus, additional – but more indirect – arguments corroborated the notion of artery-to-artery embolism as an important cause of TIAs.

- In many patients with attacks involving the cortical territory of the middle cerebral artery there is an associated lesion of the internal carotid artery, but in only very few of them is the stenosis severe enough, with a residual lumen of 1–2 mm, for blood flow to be impaired below critical levels, even assuming there is no collateral circulation.[113] In addition, the stenosis is constant but the episodes of ischaemia transient, without evidence for cardiac arrhythmias as an additional factor.
- During carotid endarterectomy, fresh and friable thrombi are seen adherent to atheromatous plaques in the carotid bifurcation, especially in patients with recent attacks.[114]
- In patients with ocular as well as cerebral attacks, the two kinds of attack almost never occur at the same time.[114]
- Manual compression of the carotid artery may lead to dislodgement of atheromatous emboli to the cerebral circulation.[115]
- If patients continue to have TIAs after occlusion of the ipsilateral internal carotid artery, there is often an additional atheromatous lesion in the common carotid or external carotid artery, these vessels being important collateral channels, supplying the hemisphere via retrograde flow through the ophthalmic artery.[106]
- Asymptomatic emboli have been seen to flash up during angiography,[116] while fibrin thrombi have been seen to pass through a cortical artery during craniotomy for a bypass procedure.[117] Transcranial Doppler monitoring has uncovered an ongoing stream of high-intensity transient signals (HITS), probably small emboli, in patients with symptomatic carotid lesions.[118] The HITS disappear after carotid endarterectomy,[119] the rate depending on the interval since operation.[120]

Whilst artery-to-artery thromboembolism from atheromatous plaques may seem the most important factor in explaining TIAs and ischaemic strokes, it is not necessarily the only one, not even in a single individual patient. For example, it is probable that emboli have especially damaging effects in vascular beds that are chronically underperfused.

2.7 Intracerebral haemorrhage

Extravasation of blood into the brain parenchyma was recognized as early as 1658 by Wepfer,[31] although we commented above that he saw the clot as an obstruction of 'vital spirits' rather than as the disease in itself, and subsequently by Morgagni.[40] The cause remained obscure, and to a large extent it still is. In 1855, before blood pressure could be measured, Kirkes observed hypertrophy of the heart in 17 of 22 patients with fatal brain haemorrhage.[121] Charcot and Bouchard in 1868 examined the brains of patients who had died from intracerebral haemorrhage and immersed these in running water; they found multiple, minute outpouchings of small blood vessels, so-called miliary aneurysms.[122] The irony of these two names being joined is that Bouchard, once Charcot's pupil, in later years generated much hostility between himself and his former chief, because he wanted to found a school of his own and to be considered the most influential man in the faculty of medicine.[123] It was in this adversarial atmosphere that in 1892 Bouchard, as president of the jury that had to judge the competition for the rank of *professeur agrégé*, did not admit Charcot's pupil Babinski.[124] Babinski subsequently left academic medicine by becoming chief of the Pitié hospital, where he devoted much time to the study of clinical signs, including the now famous 'toe sign'.[125] The aneurysms described by Charcot and Bouchard were white or brownish-coloured nodules about 0.5–2.0 mm in diameter, attached to a small arteriole, most often in the basal ganglia. At the beginning of the 20th century, Charcot and Bouchard's theory came under attack and some proposed that the primary lesion in intracerebral vessels was atherosclerosis, that most of these dilatations were not true aneurysms at all but false aneurysms caused by intramural dissection, while rupture could also occur by weakening of the vessel wall without previous aneurysm formation;[126] also some 'miliary aneurysms' may in fact have been clots in perivascular (Virchow-Robin) spaces.

Alternative explanations for the pathogenesis of primary intracerebral haemorrhage included primary necrosis of brain tissue or its vessels. Some assumed that arteries dilate and rupture only when a previous infarct had occurred, thus depriving the feeding vessel of its normal support.[127,128] The frequent coexistence of hypertension led to several theories other than plain rupture. Rosenblath postulated that a renal toxin caused necrosis of vessel walls,[129] Westphal that arterial spasm was an intermediate factor[130] and Schwartz that a multitude of terminal arterial branches became permeable.[224] In the 1960s injection techniques revived the notion

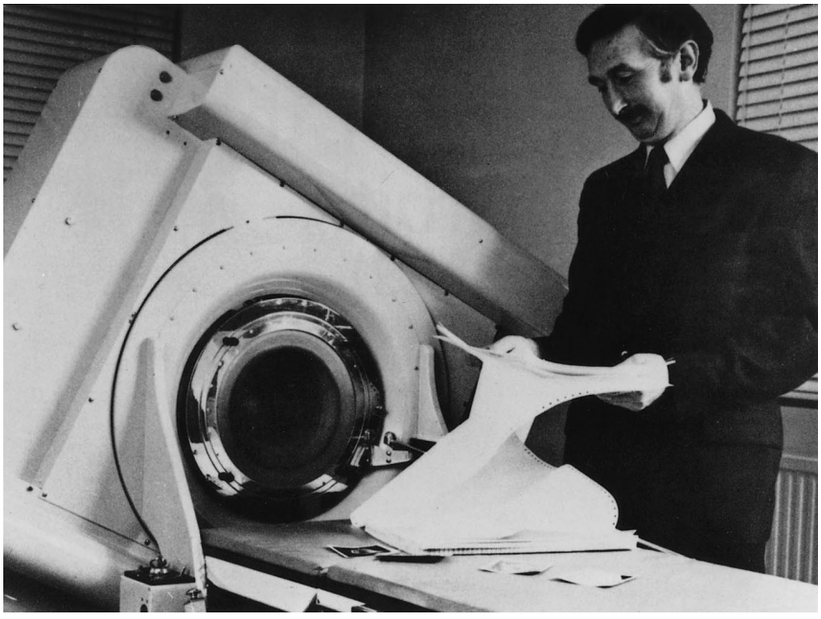

Fig. 2.9 Godfrey N. Hounsfield (1919–2004), the British engineer who received the Nobel prize in medicine in 1979 for the development of computed tomography (together with the American physicist A.M. Cormack).

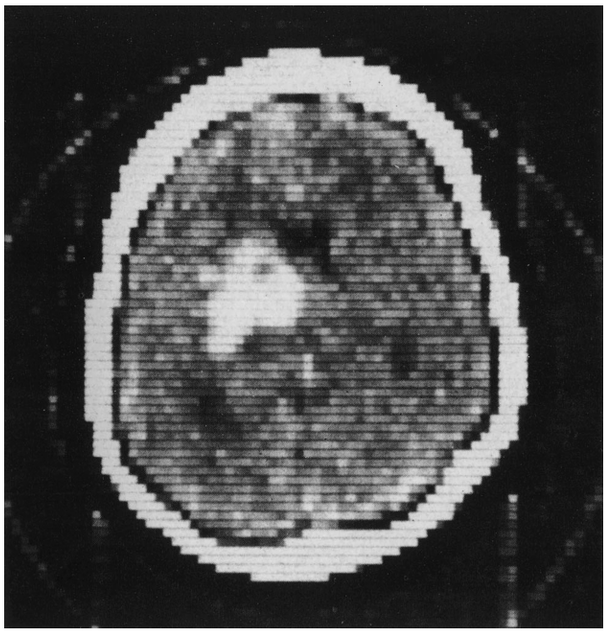

Fig. 2.10 CT scan of an intracerebral haemorrhage, from the early 1970s.[221]

of microaneurysms,[131,132] although some still suspect that the injection pressures can artifactually distend or rupture vessel walls.[133]

Amyloid angiopathy was first recognized as a cause of primary intracerebral haemorrhage in the first half of the 20th century.[134–136] This type of haemorrhage occurs especially at the border of white and grey matter and not in the deep regions of the brain that are the most common sites of haemorrhages associated with microaneurysms. The first series of such patients appeared in the 1970s.[137,138]

The invention of computed tomography by Hounsfield (1919–2004; Fig. 2.9) in the 1970s made it possible to distinguish intracerebral haemorrhage quickly and reliably from cerebral infarction (Fig. 2.10).[139,140]

2.8 Subarachnoid haemorrhage

The history of 'meningeal apoplexy' is relatively short. The disorder was not recognized until three years before the battle of Waterloo; in the following 125 years numerous accounts appeared that combined a few personal cases with attempts to review the entire world literature up to that time, the last being a heroic overview of 1125 patients.[141]

2.8.1 Diagnosis

The first unequivocal description of an aneurysm, though unruptured, was by Franciscus Biumi in 1765, who saw it not on the circle of Willis but in the cavernous sinus (at the time called Vieussens' receptacle).[8] Morgagni had also mentioned dilatations of arteries that may have been aneurysms.[40] In 1812 John Cheyne provided the first illustration of lethal subarachnoid haemorrhage at the base of the brain as a result of 'rupture of the anterior artery of the cerebrum' (Fig. 2.11), but the aneurysm that must have been the source of the haemorrhage was not recognized at the time.[45] One year later Blackall reported a postmortem observation in which the haemorrhage as well as the offending aneurysm (of the basilar artery) were identified in a 20-year-old woman.[142] The observation was coincidental, because Blackall was primarily interested in her 'anasarca' (generalized oedema, or 'dropsy'). The brain was also examined by Hodgson, who in his book on diseases of blood vessels

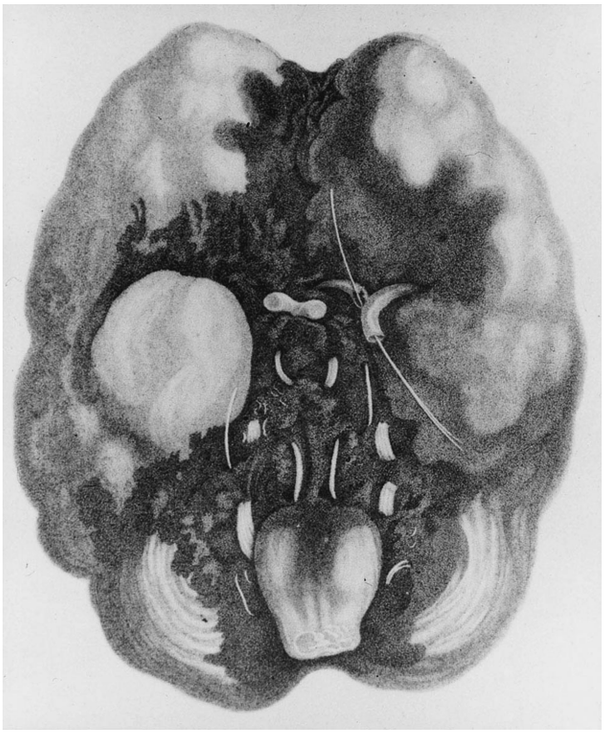

Fig. 2.11 The first anatomical illustration of subarachnoid haemorrhage, from Cheyne (1812).[45] A probe has been passed into the proximal end of the internal carotid artery and emerges at the presumed site of rupture; the offending aneurysm was not recognized at the time but presumably it was at the origin of the posterior communicating artery from the carotid artery, or at the anterior communicating artery complex.

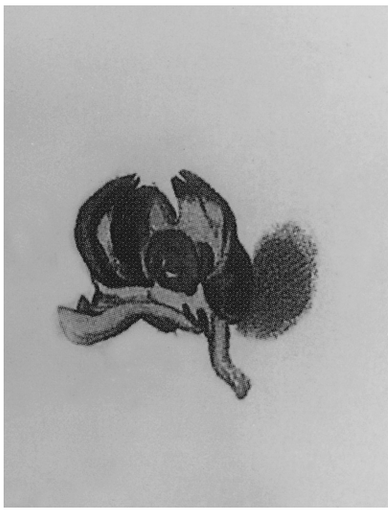

Fig. 2.12 Pea-sized aneurysmal dilatation of one of the branches of the middle cerebral artery (opened), containing a clot; the abnormality was surrounded by a large, fresh haemorrhage, which had caused the death of the 19-year-old patient, 8 days after a first episode with sudden headache (from Bright, 1831).[61]

made the point that the extravasated blood was contained under the arachnoid membrane.[143] Serres, not aware of these books, published two similar observations in a French periodical.[144] Parenthetically, it should be pointed out that medical journals, with articles about a variety of observations, did not emerge until the beginning of the 19th century, whereas the first scientific journals in general date from the middle of the 17th century.[145] In England, Richard Bright, one of the champions of the movement of 'organ-based medicine' that had started in Italy and France,[146] included an illustration of a pea-sized aneurysm on a branch of the middle cerebral artery in his richly illustrated book that appeared in 1831 (Fig. 2.12).[61] Series of other fatal cases were reported in the next few decades.[147–150]

The erroneous notion that aneurysms are congenital malformations, caused by a defect in the muscular layer of the arterial wall, was first put forward in 1887,[151] and subsequently adopted by other writers,[152,153] to be perpetuated into contemporaneous textbooks and students' minds. Turnbull also pointed out, correctly, that syphilis was an extremely rare cause of cerebral aneurysms.[153] Series of aneurysms diagnosed post mortem were often biased towards those measuring several cm,[154] or included septic aneurysms, associated with endocarditis.[155]

It took a long time before the clinical features were sorted out. In 1852 Brinton observed that fatal rupture was not the only possible presentation of aneurysms, and that other manifestations were local pressure, convulsive attacks or 'inflammation' (a rather fuzzy notion at the time).[147] The sudden onset of the headache led Lebert and Bartholow to suppose, in the 1860s and 70s, that the diagnosis might be made during life.[149,150] Lebert also observed the characteristic paralysis of the oculomotor nerve in patients before they died from rupture of an aneurysm at the origin of the posterior communicating artery from the internal carotid artery.[149] Indeed the diagnosis of ruptured aneurysm was made on two occasions in a patient with sudden headache and oculomotor palsy, by Hutchinson in England and by Bull in Norway,[156,157] but apparently these two observations had little impact.

The introduction of lumbar puncture, in 1891 by Quincke,[158] initially only for therapeutic purposes in hydrocephalic patients, led to the diagnosis of 'meningeal apoplexy' in patients who survived a subarachnoid haemorrhage.[159–161] It took another three decades before the connection with rupture of a cerebral aneurysm was made. After all, the condition was supposed to be invariably fatal since it had been recognized only after death. The 'selection bias' seems obvious in retrospect, but in our own time the same error was made with intraventricular haemorrhage – until CT scanning showed it in those who survived.

That sudden headache and meningeal haemorrhage as diagnosed by lumbar puncture could be caused by a ruptured aneurysm without fatal outcome received widespread attention only after Charles Symonds (1890–1978; Fig. 2.13) had published two landmark articles about the subject in 1923 and 1924.[162,163] It had all started in 1920, when Symonds spent some time abroad as a temporary resident in the service of the neurosurgeon Harvey Cushing (1869–1939), who had moved not long before from Baltimore to Harvard University and the Peter Bent Brigham hospital in Boston. A 52-year-old woman had been admitted with repeated episodes of headache and unconsciousness; on examination she had a right oculomotor palsy and blurring of the optic discs. A right subtemporal decompression for a suspected tumour showed recently clotted blood extending over the entire hemisphere, apparently coming from the base of the skull.[162] Apparently Symonds suggested a ruptured aneurysm as the cause.[164] When the diagnosis was confirmed at autopsy (the patient had died the day after the operation) Cushing ordered Symonds to spend his remaining time in the library to review everything on the subject: 'Either this was a fluke or there was reason in it'.[165]

The next advances were neuroradiological. The first angiographic visualization of a cerebral aneurysm during life was reported by Egas Moniz in 1933,[166] six years after the technique had been first applied.[74] In those days angiography was a hazardous procedure (involving

Fig. 2.13 Sir Charles Symonds (1890–1978).

surgical dissection of the carotid artery), to such an extent that someone like Cushing only rarely had his patients undergo it before neurosurgical exploration. Even today, in the era of selective catheterization, the risks are far from negligible. Fortunately, minimally or non-invasive techniques of angiography by means of computed tomography or magnetic resonance have largely replaced catheter angiography, at least for diagnostic purposes. The greatest leap forward in our times was the advent of computed tomography;[139] this technique made it possible to localize the extent of the haemorrhage in a precise fashion, to separate aneurysmal haemorrhage from non-aneurysmal haemorrhage and, by serial investigations, to detect and distinguish the most important complications: rebleeding, delayed ischaemia and hydrocephalus.

2.8.2 Surgical treatment

Ligation of the carotid artery has been practised since the times of Ambroise Paré (1510–1590) as a method to stop arterial bleeding in patients with neck wounds. Once

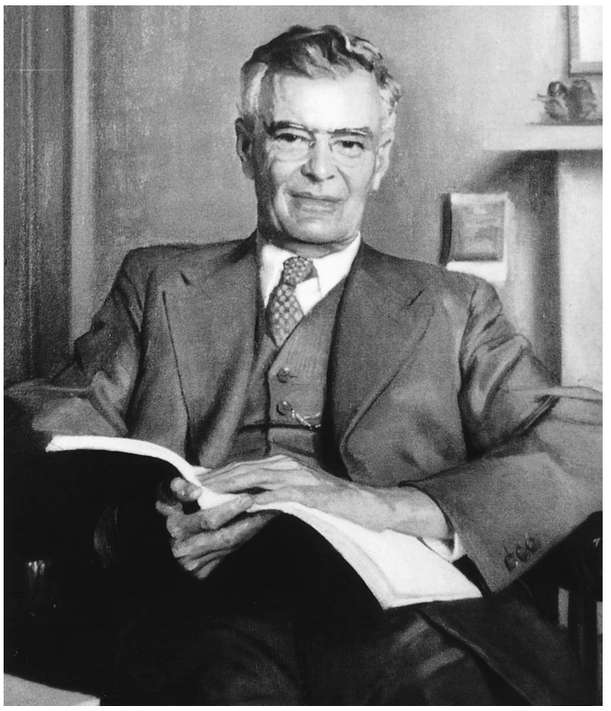

Fig. 2.14 Norman Dott (1897–1973).

aneurysms were recognized as the cause of subarachnoid haemorrhage it was a logical step to consider this procedure as a method to decrease the risk of rebleeding.[157] Hutchinson would actually have carried out the operation in 1864 had the patient not declined at the last moment, going on to survive for another 11 years.[156] Around 1886 Horsley was one of the first who actually ligated the (common) carotid artery in the neck, for a tumorous aneurysm.[154] For decades carotid ligation remained the only surgical intervention possible, but most patients were managed conservatively because the complications of surgery were considerable.[167]

In 1931 the Edinburgh neurosurgeon Norman Dott (1897–1973; Fig. 2.14), at that time only 33 years old, carried out the first intracranial operation for a ruptured aneurysm.[168] It was a more or less desperate attempt because the aneurysm had already rebled twice, leaving the patient comatose for some hours after the last episode, also with some degree of right-sided hemiparesis and aphasia. To complicate matters further, the patient was a well-known Edinburgh solicitor, 53 years old and chairman of the board of governors of the Royal Hospital for Sick Children. But, both the patient and the young neurosurgeon were prepared to take the risk.[169] About the operation Dott wrote:[170]

> A left frontal approach was employed and it was a difficult matter to elevate the tense and oedematous

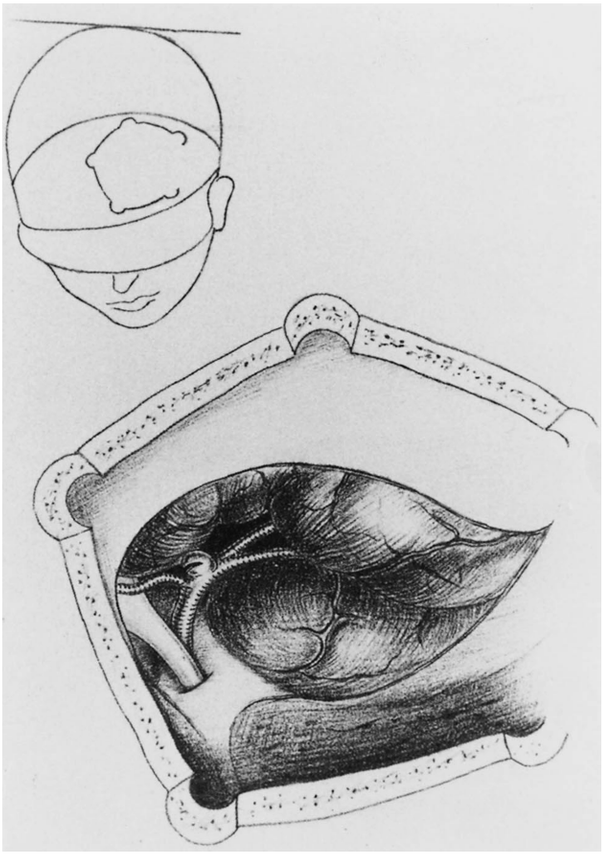

Fig. 2.15 Norman Dott's drawing of the first intracranial operation for aneurysm. The proximal middle cerebral artery aneurysm was exposed and wrapped with muscle through a left frontal flap. (From Todd *et al*., 1990;[168] by kind permission of the authors and the *Journal of Neurology, Neurosurgery and Psychiatry*.)

brain and identify the basal structures, which were bloodstained and largely embedded in clot. The left optic nerve was found and the internal carotid artery was defined at its outer side. This vessel was closely followed upwards, outwards and backwards to its bifurcation into the middle and anterior cerebral arteries. As this point was being cleared of tenacious clot a formidable arterial haemorrhage filled the wound. With the aid of suction apparatus, held closely to the bleeding point, we were able to see the aneurysm. It sprang from the upper aspect of the bifurcation junction; it was about 3 mm in diameter; blood spurted freely from its semidetached fundus. Meanwhile a colleague was obtaining fresh muscle from the patient's leg. A small fragment of muscle was accurately applied to the bleeding point and held firmly in place so that it checked the bleeding and compressed the thin walled aneurysmal sac. Thus it was steadily maintained for twelve minutes. As the retaining instrument was then cautiously withdrawn, no further bleeding occurred. The vessel was further cleared and thin strips of muscle were prepared and wound around it until a thick collar of muscle embedded the aneurysm and adjacent arterial trunks (Fig. 2.15).

The patient recovered well and a few weeks later Dott wrote, his sense of triumph carefully hidden: 'Mr Colin Black's tibialis anticus seems to have stuck well to his internal carotid – he has gone for a holiday'.[169] In later years Dott and his patient went fishing together on a number of occasions and Mr Black's neurological condition remained good until he died from myocardial infarction 11 years after the momentous operation. Unfortunately, on later occasions the outcome with a direct approach to the aneurysm was often disappointing, if not fatal, and Dott reverted to ligating the internal carotid artery in the neck or the proximal anterior cerebral artery intracranially.

In 1937 Dandy was the first to use a clip to occlude the neck of the aneurysm that had bled (Fig. 2.16).[171] Yet in some patients a clip could not be secured, and in those

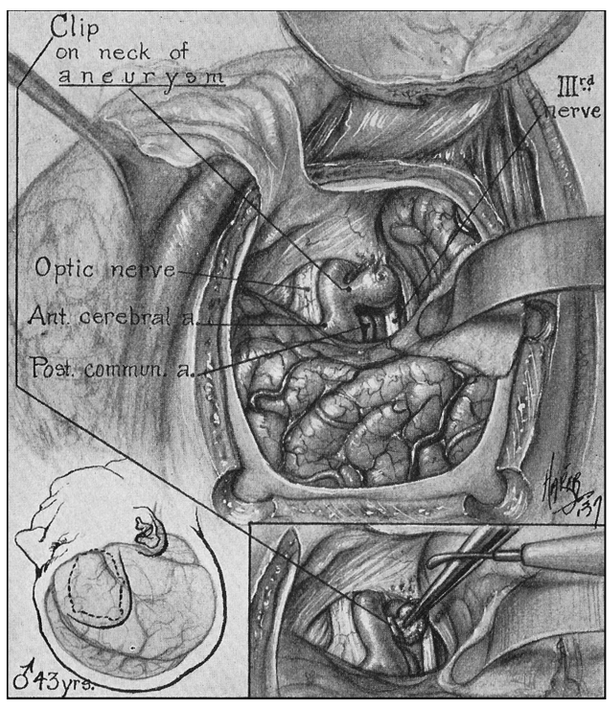

Fig. 2.16 Illustration from Dandy's 1944 monograph on intracerebral arterial aneurysms.[222] The legend is: 'Typical aneurysm of the intracranial internal carotid artery, showing the narrow neck of the sac and the bulging aneurysm; also the point of rupture. The inset shows the clip placed on the neck of the aneurysm, and the aneurysm itself shrivelled with the electric cautery.'

cases he often had to have recourse to so-called trapping, by clipping the parent vessel on either side of the aneurysm. Decades later, Drake devised a technique for approaching basilar artery aneurysms, notoriously difficult until then, and managed to apply clips to them.[172] In the 1960s, spring clips, which could be removed when placement was less than optimal, came into use and replaced the silver clips used by Dandy. Nevertheless, the direct operation of aneurysms remained dangerous and controlled trials of the efficacy of aneurysm operations were equivocal. Attempts to increase the safety of the operation included temporary cardiac arrest, hypotension and deep hypothermia, all without much success, although no formal trials were done.

In the 1980s, a consensus developed amongst neurosurgeons that direct operation of the aneurysm should best be delayed until 12–14 days after the initial haemorrhage. This regimen meant, of course, that a proportion of patients rebled or suffered other complications in the meantime. The gradual introduction of the operating microscope for aneurysm surgery in the 1970s made early operation (within 3 days) not only feasible but also fashionable, despite the dearth of evidence from controlled clinical trials. The medical management of patients with ruptured aneurysms has also improved in recent years, especially the prevention of delayed ischaemia.

In the 1980s the Italian neuroradiologist Guglielmi developed an endovascular method for occluding aneurysms by means of detachable platinum coils, initially only for aneurysms for which a surgical approach was hazardous or impossible.[173,174] In the last few years 'coiling' has largely replaced the surgical approach, provided the method is feasible for a particular aneurysm.

2.9 Treatment and its pitfalls

Doctoring has always implied treatment. In the past, medical management was almost invariably based on what later turned out to be erroneous pathophysiological concepts, and the treatments were almost invariably ineffective, if not actually harmful. Such pitiful situations are often repeated in present times, much more often than physicians and surgeons care to realize. Anyone who finds it amusing to read about 19th-century regimens, including measures such as bleeding, mustard poultices, castor oil and turpentine enemas as treatments for apoplexy, should read post-1950 treatises about the efficacy of vasodilator drugs or about transplantation of omentum to the intracranial cavity, as a chastening experience.

2.9.1 The numerical method

Before different treatments could ever be compared, it was necessary to find methods for grouping patients together and also somehow to convert disease outcomes into numbers. The Paris physician Pierre Charles Alexandre Louis (1787–1872; he survives eponymously in the *angulus Ludovici* of the sternum) is generally credited with the introduction of the numerical method in medicine. In fact his contribution was more a credo than a practical method.[175] True enough, there is the famous example of his empirical criticism of bloodletting: of 47 patients with pneumonia treated with bloodletting 18 died, against only nine of the 36 patients in the untreated group.[176] But Louis did not have the mathematical training to estimate the likelihood that a difference of this magnitude might arise by chance. It was a mathematician, Jules Gavarret (1809–1890), who criticized the analysis and conclusions of Louis's studies, although he agreed with the design.[177] Even more purely mathematical was the notion of the 'average human', an approach proposed by Adolphe Quetelet (1796–1874).

Groups and averages, these were notions that evoked not merely resistance but outright revulsion in the ranks of the established medical professionals. How on earth could one ever ignore the unique characteristics of each single individual by forcing these together into an artificial 'mean'? And how could one ever believe in a standard treatment, any more than in a standard shoe? The advent of experimental physiology intensified the opposition. The famous Claude Bernard (1813–1878) warned that one will never encounter an 'average' in nature, and that grouping of observations will obscure the true relationships between natural phenomena.[178] And the equally legendary Lord Lister (1827–1912) relied more on the theoretical basis of his antiseptic method than on the actual death rates.[179]

Until the 20th century, counting disease events was limited to population studies.[180] The beginnings of epidemiology can be traced to Sir William Petty (1623–1687), one of the founders of the Royal Society, and John Graunt (1620–1674). They worked together in collecting numerical data to describe patterns of mortality. A century and a half later, E. Blackmore reported not only on deaths but also on incident cases of disease in Plymouth.[181,182] Victorian counterparts took this further. William Farr (1807–1883), who had trained under Louis in Paris, linked self-devised classifications of diseases and occupations to population statistics at the General Registry Office. John Snow (1813–1858) mapped the

occurrence of cholera cases in the streets of London and related these to the positions of the local water pumps; these studies culminated in the famous act of Snow removing the handle from the pump in Broad Street, during the 1854 cholera epidemic. Incidentally, he later specialized in chloroform anaesthesia.[183]

The first epidemiological studies of stroke were not performed until after World War II. An early study of stroke incidence in the community was done in the UK.[184] Population-based studies addressing risk factors specifically for stroke were subsequently reported from the US (the Framingham cohort), Japan and Finland.[185–187]

2.9.2 Clinical trials

The introduction of the randomized controlled clinical trial heralded the era of 'evidence-based medicine' or rather 'organized empiricism', since medicine is not and probably will never be a positivist science like physics or chemistry.[188] Randomization in a therapeutic experiment slowly gained acceptance after the landmark UK Medical Research Council (MRC) trial of streptomycin in pulmonary tuberculosis with random assignment to treatment groups.[189] Some forerunners had already used parallel control groups. Louis (1787–1872) had been preceded by James Lind (1716–1794) in 1753 (lemons and oranges to prevent scurvy in sailors). A further step was the introduction of chance to obtain an equal balance between the experimental group and the control group. In 1898 Fibiger (1867–1928) used assignment on alternate days (injection of serum for diphtheria),[190,191] and in 1931 Amberson *et al*. flipped a coin to divide patients with pulmonary tuberculosis into those who received gold treatment and controls.[192] Blinding (or masking, as ophthalmologists prefer to say) of patients was also practised by Amberson's group, as had been done four years earlier by Ferguson *et al*. in a test of vaccines for the common cold.[193] Masking of those who were to assess outcome was advocated in 1944 by the pulmonary physicians Hinshaw and Feldman,[194] and eventually carried out in the MRC streptomycin trial of 1948. Allocation in that historic trial took place by means of randomization. An important advantage of random allocation, applied by R.A. Fisher in agriculture in the 1920s, is that it ensures equal and unbiased balancing between the two groups.[195] But the main reason why Sir Austin Bradford Hill (1897–1991), the trial's principal investigator, chose randomization is that at the same time it ensured concealment of the allocation schedule from those involved in entering patients in the trial.[196,197]

Clinical trials in cerebrovascular disease were no exception to the rule that most methodological errors have to be committed before they are recognized, as the correct solutions are often counter-intuitive. In the 1950s anticoagulant drugs seemed a rational form of treatment to prevent further strokes in survivors of (presumed) brain infarction. The same Bradford Hill who had pioneered the tuberculosis trial took the initiative for two such trials, the first in 142 and the second, with exclusion of hypertensives, in 131 patients.[198,199] There was no significant difference in the rate of non-fatal stroke between the treatment groups and controls, while there was some excess of fatal strokes, possibly haemorrhages, in patients on anticoagulants. From that time onwards anticoagulants were largely abandoned for the prevention of stroke, unless for specific indications such as a source of embolism in the heart. However, it took at least two decades before it dawned on the neurological community that the trials of anticoagulants in brain ischaemia had been too small, separately as well as collectively, to detect even large protective effects – apart from other shortcomings.[200] The same applied to an early secondary prevention trial with dipyridamole.[201]

The first intervention trial in acute stroke was with corticosteroids, by Dyken and White in 1956. They did not use randomization but stratified patients according to their clinical characteristics, and found a trend towards a higher death rate in the treated group (13/17 against 10/19 in controls), and ended up by identifying many of the methodological problems in this type of trial.[202] The first trial of carotid endarterectomy excluded surgical mishaps from the analysis;[203] subsequently the operation boomed to worrying levels, until checked by methodologically sound trials. The first large trial of aspirin in stroke prevention evoked much controversy,[204] for one thing because its initiators had chosen 'stroke or death' as the outcome event instead of stroke alone;[205] it took time for neurologists to realize that they treat whole patients rather than only their brains! Also, the initial conclusion that aspirin was ineffective for women is now a classical example of the dangers of subgroup analysis.

2.9.3 Measuring outcome: the ghost of Gall

One of the stumbling blocks in trials of acute stroke used to be the babel of tongues with regard to the measurement of outcome. Initially, so-called 'stroke scales' were applied for this aim, analogous to scales for other specific neurological conditions, such as Parkinson's disease or multiple sclerosis. Although the stated purpose of 'stroke scales' is to measure outcome, these scales are nothing but codifications of the neurological examination, while of course that examination has no other purpose than localizing lesions within the nervous system. With such a diagnostic approach, different functions of the nervous

system are separately assessed: power of limbs, speech, visual fields, etc. This reductionist, mechanistic notion of brain function reflects the localizationists' position in the scientific battle that raged in the second half of the 19th century, the opposing party believing in so-called equipotentiality.

The 'equipotentialists' believed that the brain worked as a unitary system, brain tissue being omnipotent and flexible in its function. Consequently, brain damage would result in a decrease in the overall level of performance, but not in loss of specific functions. The champion of this camp was the French physiologist Flourens, who supported his views with experiments on dogs and pigeons.[206] The alternative notion, that of localization of specific functions, was propounded in a somewhat bizarre fashion by the anatomists Gall and Spurzheim.[207] They believed that every intellectual and moral property had its own position on the surface of the brain (Fig. 2.17) and that the degree of development of these dispositions could be identified by locating overlying protuberances on the skull (Fig. 2.18). However, the theory of localization gained respectability after the stimulation experiments of Fritsch and Hitzig on anaesthetized dogs, in which they found that weak electrical currents applied through platinum electrodes to the anterior regions of the brain surface produced muscle contractions in the opposite half of the body.[208,209] The clash between the two opposing factions culminated in 1881 at the Third International Congress of Medicine, held in London.[210] The equipotentialists were represented by the German physiologist Goltz, who showed the audience a dog in which a substantial portion of the brain had been removed by means of a hose, but who could still move all four limbs, trunk and tail, and who had retained all his senses. Later, it would turn out that the lesions were less extensive than had been claimed. On the same afternoon Ferrier showed two chimpanzees, one deaf after removal of the auditory cortex, the other limping with a hemiplegic gait after extirpation of the contralateral motor area (the sight of which led Charcot to jump up and exclaim: 'Mais c'est un patient!').

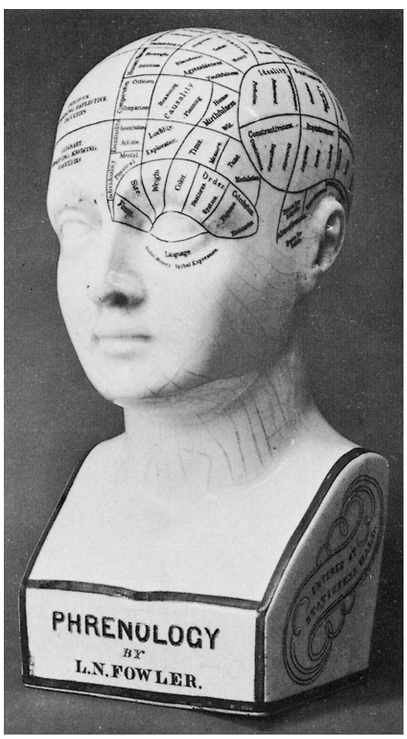

Fig. 2.17 Phrenology head (Fowler); each region of the skull is supposed to represent a mental faculty, such as 'mirthfulness', 'perception of form' or 'ideality'.

Fig. 2.18 The pseudo-science of phrenology lived on well beyond the 19th century. The Lavery Electric Phrenometer of 1907 was intended to lend modern accuracy to the measurements of bumps on the skull.[223] (Reproduced by kind permission of Cambridge University Press.)

The localizationists had won the day, but they won too completely. The greater part of the brain has no 'primary' motor, sensory or cognitive tasks, and serves to

Table 2.2 The state of an individual cannot be constructed from separate components. Imagine that you met 'the boy next door' from your childhood days after an interval of 30 years, and that your question 'How are you?' was answered with a list of details, instead of by a general statement ('fine' for example).

Profession	dentist	for 15 years
Civil state	married	wife 1.68 m, 59 kg
Bank account	positive	€9634.92
Car	Volvo	240S
Holidays	Tuscany	3 weeks
Sport	golf	handicap 8
Total ?		

connect and integrate the separate 'functions'. Similarly, everyday life consists of a multitude of tasks that are integrated and difficult to separate. Mood, initiative and speed of thinking are some of the essential features of human life that can be severely affected by stroke but are sadly ignored in 'stroke scales'. It is therefore naive to try and rebuild an entire human being from separate 'building blocks' (Table 2.2; Fig. 2.19). Patients are more than the sum of their signs. A higher, more integrated level of measurement is needed; that is, scales should measure function not at the level of the organ but at the level of the person (disability scales), or even at the level of social interaction (handicap scales). What really counts for patients is what they can do in life, compared with what they want to do or were once able to do.

2.9.4 Meta-analysis and systematic reviews

In the last quarter of the 20th century, Richard Peto and his colleagues Tom Chalmers and Iain Chalmers developed a method to overcome the problem that single studies may or may not show a significant difference in treated patients compared with controls, but that the magnitude of the difference can only be expressed as a confidence interval, which is usually wide. They collated all related trials in a given field by which the differences between the treatment group and the control group in each trial could be combined.[211] The key assumption is that, if a given treatment has any material effect on the incidence or outcome of disease, then the direction, although not necessarily the size, of this effect tends to be similar in different circumstances. If all available studies are combined, the confidence interval can be narrowed considerably and reviewer bias is avoided. There clearly was a pressing need for up-to-date systematic reviews of all the available evidence regarding the various aspects of care of stroke patients – indeed, of all medical interventions. This need led to the Cochrane Collaboration, which includes a stroke review group.[212]

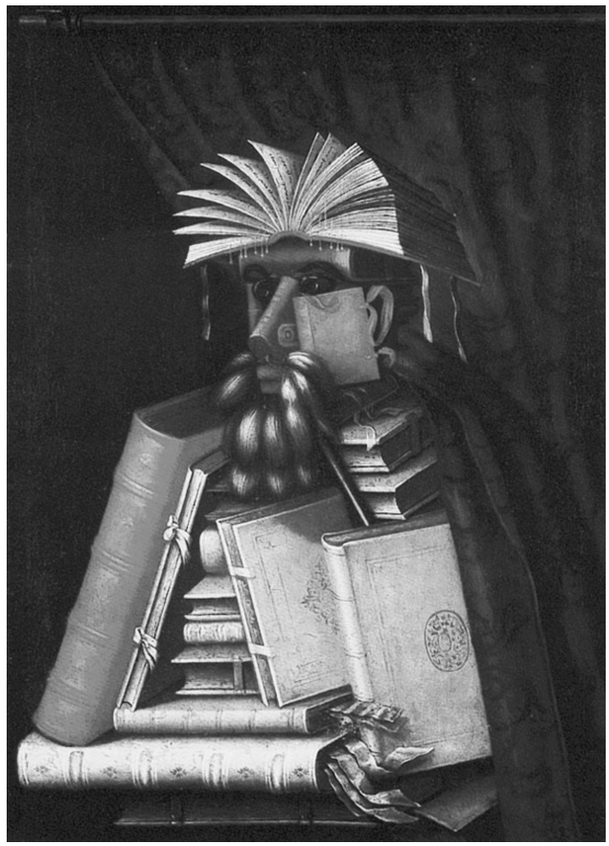

Fig. 2.19 The librarian (1566), by Giuseppe Arcimboldo (1530–1593). Oil on canvas, 97 × 71 cm. (By kind permission of Skokloster Castle, Sweden.)

The graphic representation of systematic reviews started in 1978, with simple lines to depict 95% confidence intervals.[213] In 1982 Lewis and Clarke had the idea to combine the separate estimates into an overall estimate, at the bottom of the figure.[214,215] Subsequently Richard Peto's group solved the paradox that small trials were most conspicuous because of their large confidence intervals, by putting a square at the site of the point estimate, the size of the square being proportional to the power of the trial (Fig. 2.20).[216] These graphs have since become known as 'forest plots', probably because the many lines might be seen as trees.[215]

2.10 Epilogue

Despite the many advances in the knowledge about stroke that we have highlighted, our story could not but

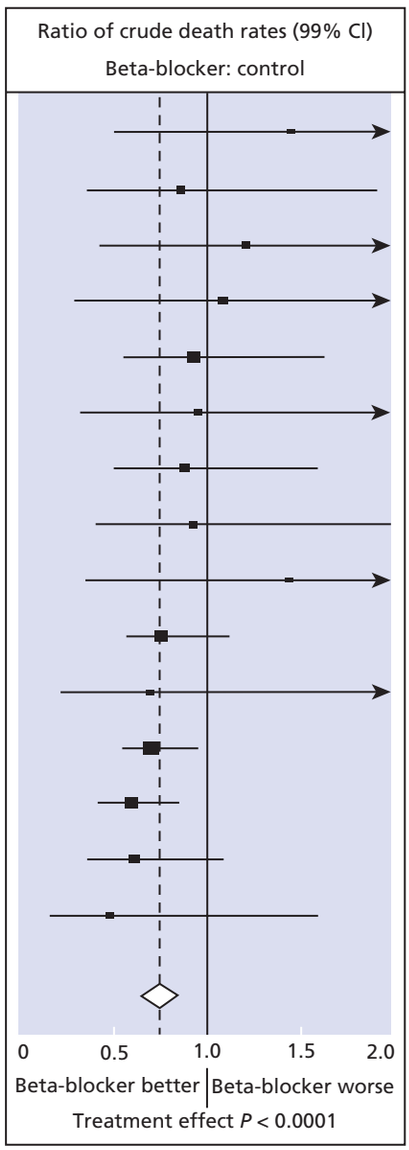

Fig. 2.20 'Forest plot'. Figure redrawn after Lewis and Ellis's original plot from 1982, which for the first time combined 99% confidence intervals of different placebo-controlled clinical trials of beta blockers after myocardial infarction.[214] This modern variant shows the results of each component study as a square centred on the point estimate of the result of each study; the size of each square is proportional to the amount of information provided in that trial. A horizontal line runs through the square to show its confidence interval (CI). The overall estimate from the meta-analysis and its confidence interval are put at the bottom, represented as a diamond.[215] (Reproduced by kind permission of the BMJ Publishing Group.)

remain anachronistic and fragmented. It is extremely difficult to try and stand in the shoes of one's forebears, because to achieve this the mind should be cleared from all knowledge obtained since their time.[217] For those of us who can think back as small a time span as three decades, what diagnosis did we make, in those times, in patients we now know to have survived carotid dissection or intracranial venous thrombosis, to name but two examples? Heaven only knows. In the same way, not so much longer ago, it was impossible to distinguish haemorrhage from infarction; or haemorrhage from some mysterious other condition that mimicked haemorrhage but in which the brain looked practically normal; or stroke from other brain diseases; or even stroke from heart disease. Necessarily our account has been anecdotal. In reality the progress of science is slow and continuous, not a succession of breakthroughs. This also applies to the few decades we have witnessed during our own careers. We do not expect a sensational novelty when we walk into hospital tomorrow, but a lot has changed since we were medical students. This refers not only to the body of medical knowledge but also to the methods of medical research. Empirical testing has gained ascendancy over pathophysiological theory, for the treatment as well as the prevention of disease. The rate of change is a bit like the shifting position of the sun across the sky: one cannot see it move, but there is a dramatic sweep between dawn and sunset. We expect to see many more dawns in stroke research.

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