Section I

General Features of Cerebrovascular Disease in the Posterior Circulation

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Chapter 1

Historical background

The past is always with us, never to be escaped; it alone is enduring; but amidst the changes and chances which succeed one another so rapidly in this life, we are apt to live too much for the present and too much in the future.
Sir William Osler, Aequanimitas, 1889

We cannot afford to repeat the history of neurology every ten years.
Charles Miller Fisher

The management of stroke patients today is more complex and difficult than at any time in the past. Clinicians today use more precise and effective diagnostic technologies and have access to more varied, more potent, and probably more hazardous medical and surgical treatments than was ever previously possible. Advances in technology, new tests, results of new clinical studies and trials, and the results of basic and clinical research are reported almost daily. Keeping up with these rapid advances is difficult. Maintaining a sense of proportion and a broad perspective that sees and appreciates the forest amidst the trees is even more problematic.

In order for clinicians to place the present ideas, capabilities, diagnoses, and treatments into perspective, it is essential for them to be familiar with the historical background in the field. If clinicians are to know *where they are* and *where they are going in the future*, they must know *where they and their predecessors have been.* History adds a broadening dimension to knowledge. For this reason, I begin this monograph on posterior circulation stroke with a historical review that outlines the development of ideas concerning cerebrovascular disease in general and then specifically about vertebrobasilar hemorrhage and ischemia. It is impossible to consider the posterior circulation in isolation without first covering stroke in general. The carotid and vertebrobasilar circulations cannot and should not be completely separated since knowledge and advances in each always affects the other. Herein I plan a very broad but relatively concise overview meant to capture the main historical highlights. My intent is not to compulsively register each contribution or to give credit to all important reports. Instead, I want to construct an outline that will help clinicians understand the present state of knowledge. The past should help to focus and broaden the perspective of the present and the future. I begin with a brief review of the early history of stroke. Discussion of the development of general knowledge about stroke during the nineteenth and early twentieth centuries should set the stage for coverage of more focused analysis of the recent history of posterior circulation stroke. In Section II and Section III of this monograph, I will elaborate in much more detail on historical aspects of the conditions discussed in each chapter.

Early history

The writings of Hippocrates (460–370 BC) probably contain the first clear descriptions of stroke. Hippocrates and his followers emphasized clinical observation and prognostic

indicators.[1–4] In his aphorisms on apoplexy, Hippocrates wrote that apoplexy was most common between 40 and 60 years of age, and attacks of numbness might reflect "impending apoplexy."[5] He described the poor prognosis of patients who suddenly spontaneously developed headache and coma (probably referring to subarachnoid hemorrhage). One of his descriptions was of a woman who had headache, right arm weakness, and an inability to speak in her third month of pregnancy.[3] Hippocrates observed that there were many blood vessels that were connected to the brain most of which were thin, but two (the carotid arteries) were thick. The Greeks in the time of Hippocrates knew that interruption of these blood vessels to the brain could cause loss of consciousness, so they called these thick arteries *carotid* from the Greek word *Karos* meaning deep sleep.[3]

Aurelius Celsus (25 BC – AD 50) differentiated apoplexy from other paralytic states. In apoplexy, the weakness was sudden in onset and was localized to one part or one side of the body while, in paralysis, the disorder was more gradual in onset and more generalized.[3] Areteus of Cappadocia broadened the concept of apoplexy to include paralysis of sensation and understanding as well as movement.[3] He recognized that paralysis developed on the side of the body opposite to the side of the head affected.[2,3]

Galen (AD 131–201), with his voluminous writings and authoritative style, dominated the 1300 years that followed his death. His early writings emphasize observations and experimentations.[4] He wrote of the abruptness of the onset of apoplexy. An apoplectic suddenly became senseless as if struck down by lightning with loss of all motion except respiration.[3] In these early writings, authors described the outward phenomenology of sudden brain dysfunction. These changes could be noted by talking to the affected person and while observing him or her while fully dressed. Demographic, geographic, and epidemiological features were also studied. The main concern was *prognosis* for, at that time, the worth of a physician was judged by the ability to predict outcome. Treatment involved mostly advice about general health measures. Little was known about the nature and causes of the conditions described.

Anatomy and pathology: the sixteenth, seventeenth, and eighteenth centuries

Galen's anatomical studies probably involved dissection of animals not humans.[4] In the century that followed, most physicians relied on the writings of Galen rather than on their own observations or experiments.[4] Andreas Vesalius (1514–1564) challenged this long tradition by dissecting *human* cadavers and relying on his own eyes and observations rather than on the galenic writings and pronouncements.[4] His great book, "the *Fabrica*" (*De humani corporis fabrica*),[6] contained 15 detailed anatomical plates that illustrated the brain and its anatomy and vascular supply.

Thomas Willis (1621–1675) added much more detail on the anatomy of the extracranial and intracranial arteries.[7] Willis clearly described collateral circulation in the head and neck: "the cephalic arteries, whether they be carotid or vertebrals, communicate one with the other reciprocally in various ways… This we have demonstrated by injecting dark substances in only one branch and observing that the whole brain becomes colored."[8] He also illustrated and described the polygonal arrangement of arteries at the base of the brain that is now referred to as the circle of Willis. Willis suggested that, in the individual patient, the anatomical composition of arteries at the base of the brain influenced the presence and severity of apoplectic paralysis.[3] Much later, during the late nineteenth and early twentieth centuries, investigators throughout Europe, including Duret, Foix, and Stopford, would return to more detailed studies of the brain's vasculature.

In 1658, Johann Jacob Wepfer (1620–1695), a German physician from Schaffhausen, wrote a popular and detailed treatise on apoplexy.[9] Wepfer followed the example of Vesalius and performed meticulous examinations and dissections on the brains of patients dying of apoplexy. Wepfer described the appearance of the internal carotid artery in the siphon and the course of the intracranial arteries. Blockage of the carotid or vertebral arteries was recognized as a cause of apoplexy, the obstruction preventing entry of sufficient blood into a portion of the brain. Wepfer was the first to clearly show that hemorrhage into and around the brain was an important cause of apoplexy. Wepfer distinguished two types of apoplexy: in one form, the supply of blood to the brain was obstructed or precluded, and in the other, animal spirits escaped.[8–10] By the latter he implied bleeding. Wepfer included in his treatise the findings in four patients with hemorrhage, subarachnoid and intracerebral.

During the eighteenth century, the publication of a single work, *De Sedibus* (*De Sedibus et causis morborum per anatomen Indigatis)* by Morgagni in 1761, led to a dramatic change in the direction of investigation and thought in medicine and neurology.[4,11] Giovanni Battista Morgagni (1682–1771) was a renowned professor of anatomy at the University of Padua in Italy. He collected material during his entire career for his epic work, which was published when he was 79 years old. Morgagni believed that the secret to understanding disease was to carefully study humans at necropsy and to correlate the pathology found with symptoms during life. Clinicians now take the clinicopathological correlation method for granted but it was a new approach for physicians of the eighteenth century.

De Sedibus was organized into five volumes consisting of letters written to a young man describing each case in the collection. The first book was called *Diseases of the Head.* Morgagni's descriptions of symptoms and the circumstances surrounding the symptoms were very vivid. He also described the pathological findings in detail. Morgagni thought that the extravasation of blood found in the cranium was from an aneurysmal dilatation of the arteries and an enlargement of their delicate coats.[2] The soft brain substance yielded to the impulse of blood, causing apoplexy. Blood-filled cavities could rupture into the ventricles or onto the outer brain surface.

Before Morgagni, there were no detailed systematic clinical-pathological studies or atlases. Wepfer's treatise on apoplexy came close but much of that work was speculative and theoretical and was not based on systematic data collection and analysis. After Morgagni, the way was open for observation, necropsy examinations, and analysis of data. Emphasis had shifted from the study of normal anatomy to inquiry about diseases and their appearances, causes, and the associated clinical findings during life. The modern era had begun.

The nineteenth and early twentieth centuries

John Cheyne (1777–1836), a prominent Irish physician, wrote an influential treatise on apoplexy that was published in 1812.[12] Cheyne sought to separate the phenomenology of lethargy from apoplexy. Following the lead of Morgagni, Cheyne included in his treatise detailed clinical descriptions of patients, as they would be encountered socially in their usual attire, and the appearance of brains at necropsy. After reviewing the history of writings on apoplexy and its treatment (emetics, bloodletting, purges, external applications, etc.), Cheyne described 22 cases. Plates illustrated the "morbid appearances" of the brains. Cheyne described brain softening and both intracerebral and subarachnoid hemorrhages. In some patients who survived their apoplectic attack for some time, Cheyne found cavities filled with rusty yellowish serum within the brain at necropsy. Cheyne surmised that the cavities were lined by a membrane that was able to absorb red blood cells. One patient described by Cheyne had a pontine hematoma. Case 14 was a "carpenter, 35 years of age, phlegmatic, pale, muscular, not habitually intemperate." He suffered from severe headaches and, after one such headache, he vomited and soon after "became insensible." About an hour later, his breathing became irregular and he was deeply comatose, and soon dead.[12] Cheyne described this man's brain as follows: "In dissecting the base of the brain, there was discovered, formed by rupture in the substance of the pons varolii, a collection of dark clotted blood, in an irregular cavity, having a ragged surface and communicating with the fourth ventricle which was full of blood."[12]

Following the lead of Morgagni and Cheyne, during the second quarter of the nineteenth century, there was an outpouring of atlases that illustrated pathological findings. Robert Hooper published the first of these atlases, which contained some plates of brain lesions including cases of putaminal and pontine hemorrhages.[13] The atlases of Cruveilhier (published 1835–1842),[14] Carswell (1838), and Richard Bright (1831)[15] contained detailed lithographs illustrating pathology and neuropathology. Bright, a leading British consultant who worked at Guy's Hospital in London, was very interested in the brain although today he is better remembered for his work on the kidney. Volume 2 of Bright's *Reports of Medical Cases*, entitled *Diseases of the Brain and Nervous System*,[15] was published in 1831. Bright had collected more than 200 neuropathological cases and illustrated 25 of these in color prints in this volume. Vascular cases were included. Bright also published in 1836 a paper on the clinical and necropsy findings in patients with abnormalities of the arteries of the brain.[16]

During the nineteenth century, the general physical and neurological examinations, as we now know them, developed. After the introduction of the stethoscope by Rene Laennec (1781–1826) into clinical medicine, auscultation of the chest and heart became routine, and patients were examined for the first time without clothing.[4] Before this era clinical descriptions, for example, those of Morgagni, Wepfer, and Cheyne, were mostly observations and appearances of fully dressed individuals and included no physical examinations. Jean Martin Charcot (1825–1893) working at the Salpêtrière hospital in Paris probably deserves the most credit for developing the clinical neurological and ophthalmological examinations. His pupil Babinski elaborated on further details of the neurological examination, especially reflexes. Sir William Gowers (1845–1915), working in London at the National Hospital for Nervous Diseases at Queen Square, also elaborated on the neurological examination and described the most common and important findings in patients with various neurological diseases.[17] The modern era of careful clinical examinations, descriptions of phenomenology, and meticulous neuropathology was well developed by the early years of the twentieth century. Well-known clinicians such as Gowers, Sir William Osler, and Kinnier Wilson wrote textbooks describing the major clinical and pathological findings in most neurological diseases including stroke.

Development of knowledge about the causes of stroke

Ischemia

Clinicians now take for granted the concept that infarction is due to lack of blood supply and nutrition caused by blockage of arteries supplying the areas of ischemia. But early observers referred to focal necrotic regions using such nonspecific descriptive terms such as softenings, ramollissements, and encephalomalacia. These softenings were not clearly attributed to ischemia until the middle of the nineteenth century.[18] Physicians had known about coagulation within the vascular system for centuries. Vesalius described in 1543 "unnatural deposits" within the left atrium in patients with gangrene of the extremities.[6] Diseases of vessels were also well described. Wepfer had noted firm fibrous masses within the walls of arteries.[9,10] Willis also had described cases in which "both carotid arteries were choked up so that not the least drop of blood could pass through either of them."[10] Others also found thrombi and coagula in the vascular system at necropsy but debated whether or not these formed post mortem or during life. During the late eighteenth and early nineteenth centuries, two major figures, John Hunter in England and Cruveilhier in France, thought that coagula were caused by inflammation in the veins.[18] Hunter, writing in 1793, noted the frequency of vein inflammation after surgery and after phlebotomies and postulated that venous thrombi formed as exudates from the walls of blood vessels.[18,19] If adhesions did not form, the clots could be

Figure 1.1. Dr. Rudolph Ludwig Carl Virchow

swept into the general circulation. Cruveilhier, in 1829, wrote that coagulation in veins was the earliest sign of phlebitis.[18] Thrombi within arteries and the heart were attributed at that time to a similar inflammatory arteritis.

Rudolph Virchow (1821–1902) (Figure 1.1) deserves the major credit for describing the process of in-situ antemortem thrombosis with subsequent embolism. In a remarkable series of observations and experiments, Virchow analyzed the relationship between thrombi and infarction, locally and at a distance. Among 76 necropsies performed in 1847, Virchow found thrombi in the veins of the extremities in 18 patients and within the pulmonary arteries in 11.[18,20] Virchow reasoned that the bloodstream emanating from these veins must have been the conduit for transportation of these thrombi to distant sites like the lung arteries. He then used animal experiments to study the fate of foreign materials placed in the veins. Virchow then sought and found obstruction of brain, splenic, renal, and limb arteries at necropsy in patients who had cardiac valve disease and left atrial thrombi. Virchow thus systematically proved that in-situ thrombosis and embolism were the cause of infarction and that the process was not dependent on inflammation. Despite this demonstration by Virchow, physicians did not appreciate the clinical features of coronary thrombosis and myocardial infarction until the report of James Herrick in 1912,[21] and cardiologists did not clarify the relationship between angina pectoris, coronary artery occlusion, and myocardial infarction until the 1940s.[22]

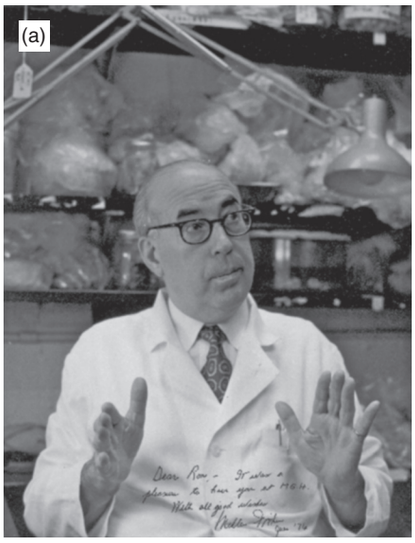
Interest in the causes of *brain ischemia* probably began with Wepfer who recognized that, at necropsy, there was often an obstruction of blood flow caused by disease of arterial walls. Abercrombie included a section on apoplexy in his 1828 treatise on diseases of the brain and spinal cord, in which he discussed the clinical and pathological features.[2,23] He described opaque osseous-like arterial constrictive lesions. Abercrombie suggested that spasm of arteries and narrowing of arteries with interruption of circulation and vascular rupture were possible mechanisms of apoplexy.[2,23]

Chiari in 1896 described a single patient who had an intra-arterial embolism that had apparently arisen from a thrombus in the internal carotid artery in the neck,[24] but this observation went unnoticed until Miller Fisher's landmark paper on internal carotid artery occlusion which appeared in 1951.[25] Charles Foix (1882–1927) and his French colleagues, during the 1920s, analyzed the distribution of brain softenings (ramollissements) in various arterial territories and correlated the anatomy with the clinical findings.[26] The early writings of Foix were concerned mostly with vascular anatomy, distribution of infarcts, and clinical-anatomical correlation. Only a few weeks before his premature death, Foix and his colleagues Hillemand and Ley presented a very preliminary report to the Medical Society of the hospitals of Paris on the vascular pathology found in arteries supplying regions of brain softenings.[27] Among 56 cases, the artery supplying the infarct was completely occluded in only 12 patients, subtotally occluded in 14, but in 30, the supply artery was widely patent. Foix and his colleagues proposed four possible explanations for the frequent lack of arterial occlusion at necropsy: (1) occlusion might *follow* brain softening and might have developed later; (2) embolism with passage of embolic material by the time of autopsy; (3) insufficiency ("l'insuffisance cardio-arterielle"), that is, more proximally located circulatory failure; and (4) vasospasm ("spasme arterielle").[26,27]

Miller Fisher's report on carotid artery occlusion published in 1951 emphasized the occurrence of intra-arterial embolism arising from proximal arterial occlusive lesions as a very important cause of ischemic stroke.[25] Also, in this paper, Fisher noted the very frequent occurrence of temporary warning episodes, which he dubbed transient ischemic attacks (TIAs), that preceded and presaged later strokes. Prior to Fisher, a few scattered mentions of transient warning spells can be found in the literature but practicing physicians in 1950 were generally unaware of their existence. Figures 1.2a and b are photographs of Dr. C. Miller Fisher in his laboratory and examining a patient and Figure 1.3 shows Dr. Fisher with the present author.

Thomas Willis in 1679 had alluded to intermittent minor dysfunctions that preceded apoplexy.[28] Hunt in a discussion of the role of the carotid artery in causing brain ischemia mentioned attacks of transient hemiplegia.[29] In their textbooks of Medicine and Neurology, Gowers[17], Oppenheim, and Osler[30] had also briefly mentioned transient warning episodes[28] but no one had attempted to define the causes of these TIAs or to emphasize their importance as a window of opportunity to begin treatment to prevent subsequent stroke.

More recently, studies have documented the great importance and ubiquity of intracranial embolism, both cardiogenic and intra-arterial, in the causation of transient brain ischemia and infarction. In the Harvard Stroke Registry, angiography performed within 48 hours after onset of symptoms of ischemic stroke showed a high incidence of intracranial arterial occlusion, while studies after 48 hours were often normal.[31] Ringelstein and colleagues studied the pathogenesis of brain infarcts in 107 patients with internal carotid artery occlusions in the neck.[32] Angiography in 15 of 21 patients (71%) showed an "occlusio supra occlusionem", that is, intra-arterial emboli



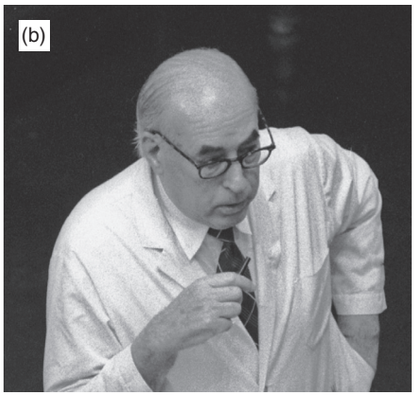


Figure 1.2. (a) C. Miller Fisher in his laboratory. (b) C. Miller Fisher examining a patient. Kindly submitted by Dr. Ron Kobayahi

Figure 1.3. C. Miller Fisher with Louis R. Caplan, 1994

blocking intracranial arteries.[32] Fieschi *et al.* performed angiography within 6 hours of onset of symptoms of brain ischemia and showed complete arterial occlusions by thrombi in 76% of patients, the majority of which (66%) were intracranial.[33] In one study of patients screened for acute treatment with recombinant tissue plasminogen activator (rtPA), 112 of 139 patients (80%) had arterial occlusions on angiography performed within 8 hours of symptom onset.[34,35] In a study of fibrinolytic treatment of patients with acute brainstem ischemia, a high proportion had occlusions within the intracranial posterior circulation.[36] Monitoring of the intracranial arteries of patients using transcranial Doppler ultrasound (TCD) has begun to show a very high frequency of intracranial embolism in patients with potential donor sources of embolic materials.[37]

Study of potential donor sites also has shown a high frequency of thrombi and lesions known to predispose to thrombus formation. Fisher and Ojemann meticulously studied and analyzed a large number of carotid endarterectomy specimens.[38] Most patients with severe stenosis had mural thrombi or platelet–fibrin aggregates within arterial ulcerations, irregularities, and crevices. Echocardiography often shows valvular disease, mural thrombi, hypokinetic or aneurysmally dilated areas of myocardium, dilated left atria, and protruding aortic atheromas.[37] Necropsy and echocardiographic studies have shown that the aorta is a very important and relatively common donor source of brain embolism.[39–41] In the carotid and vertebral arteries thrombi most often form in regions of atherosclerotic plaques but some patients who have fresh intraluminal thrombi have a coagulopathy that caused or potentiated thrombosis.[42–44] Arterial dissections in the neck arteries have also become well recognized as sources of intra-arterial brain embolism.

Pathological and clinical studies, at first using dye contrast catheter angiography and later with CT and MR angiography and ultrasound, showed a high frequency of extracranial occlusive disease in the carotid and vertebral arteries in the neck in white men, especially those with hypertension, a history of smoking cigarettes, hypercholesterolemia, and coexistent coronary and peripheral vascular occlusive disease.[31,45] In blacks, and individuals of Chinese, Japanese, and Thai ancestry and in women, there is a higher incidence of intracranial occlusive disease.[45]

Although Durand-Fardel in 1843[46] and Pierre Marie[47] and Ferrand[48] in the first years of the twentieth century had described small, deep infarcts – lacunes – these lesions did not become well known until the work of Fisher during the 1960s.[49] Fisher showed that degenerative changes in penetrating cerebral and brainstem arteries in the form of lipohyalinosis and microatheromas caused these deep infarcts.[50] Fisher and his colleagues and students described the pathology and the various clinical syndromes associated with lacunar infarction,[49,51–53] and distinguished the pathology found in penetrating arteries from atheromatous disease of larger extracranial and intracranial arteries and from cardiac origin embolism as different mechanisms of ischemic stroke. More recently newer magnetic resonance and CT technology has made it possible to image in vivo large intracranial arteries and to define the volume and location of plaques and to show plaques that block the orifices of penetrating branch arteries.[54–56]

Hemorrhage

During the latter part of the nineteenth century, interest turned to the nature and causes of brain hemorrhage. In 1873, Lidell,

a surgeon and anatomist, included a section on cerebral hemorrhage in his treatise on brain diseases.[57] Lidell's description of the main gross pathological features of brain hematomas is applicable even today.

> Size of the clot varies from that of a hemp-seed to that of the fist. If the extravasation occurs in the vicinity of a ventricle, it often breaks through the walls of the latter, and flows therein. Extravasations forming near the surface of the brain not infrequently break through the cortical substance and escape into the subarachnoid space. Usually there is only one hemorrhagic effusion in the whole brain, occasionally several. The most frequent seat of these effusions is the corpus striatum, the thalamus opticus, and the large medullary masses of the cerebral hemispheres; less frequently, they occur in the cortical substance of the cerebrum, the cerebellum, and in the pons varioli.[57]

It was well known in Lidell's time that spontaneous hematomas usually occurred in the putamen, thalamus, lobar white matter, cerebellum, and pons, and the gross appearance and drainage patterns of these hematomas were described accurately. Charles Bouchard (1837–1915), a young physician and researcher working in the laboratory of the great French neurologist, Jean Martin Charcot (1825–1893), sought the origin of these brain hematomas.[2] Charcot and Bouchard found tiny aneurysms within large intracerebral hematomas in 3 of 84 patients with fatal strokes. They also found small lesions that resembled tiny globules of grain along many penetrating arteries.[58,59] These so-called "miliary aneurysms" were described in detail and liberally illustrated. Bouchard later published his ideas and findings in a monograph on brain hemorrhage.[60] I find Bouchard's description of these aneurysms confusing since he seems to be describing vascular lesions that are grossly visible after the bulk of the hematoma is removed. However, more recent illustrations and subsequent analysis interpret the aneurysmal dilatations that Charcot and Bouchard found as microscopic and different in appearance from commonly available sketches of the lesions made by Bouchard in his book.[60]

Although less well known, Bouchard was one of the first to provide evidence that arterial hypertension might be an important cause of brain hemorrhages. He reviewed the evidence that left ventricular hypertrophy and "a state of rigidity of the main arterial trunks or some obstacles to the flow of blood" were common in patients with intracerebral hemorrhage (ICH).[60] Wepfer, in 1658, had alluded to a predisposition for apoplexy in those "whose faces and hands are livid,"[9] and Cheyne in 1812 noted vascular congestion, an "excitement of the arteries of the brain," in his treatise.[12] One of Cheyne's patients had severe headache, attributed by the author to possible hypertension, before his fatal pontine hemorrhage.[12] Recall that sphygmomanometers were not introduced into clinical medicine until the early part of the twentieth century so that earlier physicians had no way to measure blood pressure clinically.

Henry Duret (1849–1921), a French neurosurgeon, began to study meticulously and describe the anatomy of the arteries to the brain.[2,61,62] He studied more than 200 brains in Charcot's laboratory at the Salpêtrière in Paris and identified the common sites of brain infarcts and hemorrhages. Duret accurately mapped and illustrated the distributions of the anterior, middle, and posterior cerebral arteries and the usual distribution of deep branches to the basal ganglia, thalamus, and brainstem.[2,61,62] With Charcot, he described the lenticulostriate artery and called it "the artery of cerebral hemorrhage."[2] Duret was also very interested in brain trauma.[63] In reviewing specimens of patients who died of head injury and traumatic brain hemorrhages, he became aware that many had hemorrhages in the upper brainstem near the midline (so-called Duret hemorrhages). Duret posited that these brainstem lesions were related to sudden increase in intracranial pressure and not to the primary injury.[63]

English-speaking physicians and students who sought information about stroke and other neurological diseases, during the first quarter of the twentieth century, would have consulted the popular textbook of neurology by Sir William Gowers[17] and the textbook of medicine written by Sir William Osler.[64] Gowers began his coverage of ICH by discussing etiology. "Hemorrhage is always due to rupture of a vessel."[17] Gowers noted that the vessel ruptured was nearly always an artery and rupture was caused by an injury or "internal causes." Gowers cited hypertension as a predisposing cause with additional "exciting causes" superimposed at the time of the bleeding. Gowers wrote: "When the wall of an artery is weakened, it yields before the blood pressure and becomes bulged."[17] This description refers to the miliary aneurysms described previously by Charcot and Bouchard. Gowers thought that these vascular lesions were a very important cause of brain hemorrhage. Writing about immediate exciting causes, Gowers wrote that "the actual rupture sometimes occurs during some temporary increase in blood pressure that might accompany physical effort or activity or be provoked by emotional stress."[17] More recent studies show that acute elevations in blood pressure can cause ICH.[65] Gowers and Osler both described the common locations of spontaneous hemorrhages – putaminal, thalamic, pontine, and cerebellar. Onset was usually abrupt with invariable headache and stupor as well as focal neurological signs. Mortality was very high.

Gowers and Osler each emphasized the great difficulty in differentiating brain infarction from hemorrhage during life. In 1935, Charles Aring and Houston Merritt reported an analysis of 245 patients with strokes studied at necropsy and clinically at the Boston City Hospital.[66] The authors analyzed the demographic, epidemiological, historical, and clinical data to see which features differentiated thrombosis from hemorrhage. Key features that favored hemorrhage were headache, vomiting, decreased level of consciousness, progression of the deficit, bloody spinal fluid, and increased spinal fluid pressure.[66] Since only fatal strokes were included, this series was biased toward only those patients with large hemorrhages.

Miller Fisher was able during the middle years of the twentieth century to collate prior data, to make new clinical and pathological observations, and to summarize extant information about ICH.[67,68] Necropsy studies convinced Fisher of the presence of small hematomas that often appeared as

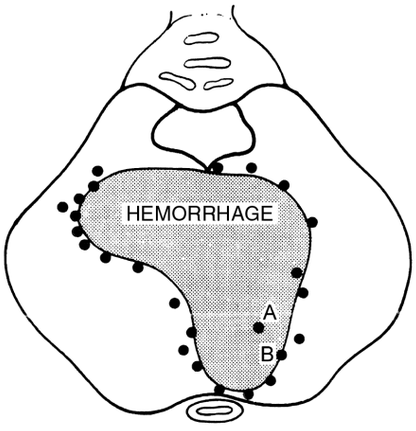


Figure 1.4. Miller Fisher's drawing of the location of fibrin globes (black dots) along the circumference of a pontine hemorrhage. From reference 69 with permission.

small slit-like cavities stained by hemosiderin. Although these hematomas were not "harmless," clearly patients often made good recoveries.[67] Recall that before Fisher most clinicians thought of brain hemorrhage as a uniformly fatal or devastating condition. Studying some hematomas in serial section, Fisher noted that small globoid caps were situated around the circumference of the hematoma. These caps represented bleeding capillaries or small arterioles.[69] Figure 1.4 is a diagram that Fisher made of the bleeding globes in a patient who died of a pontine hemorrhage.[69] Fisher interpreted the circumferential bleeding sites as evidence that the hematomas probably developed gradually with pressure effects beginning and maximal at the center of the hematomas and causing secondary pressure damage sequentially to vessels on the periphery of the expanding hematoma. Hemorrhages would begin small. Pressure in the center exerted force on vessels at the periphery, causing them to bleed. The hematoma grew on its outer circumference much like a snowball rolling downhill. This process of growth of the hematoma would stop if and when the hematoma drained onto the pial or ventricular surface and, in so doing, partially decompressed itself. Alternatively, tissue pressure and intracranial pressure external to the hematoma would increase until pressures internal and external to the hematoma equalized.

The clinical course of patients with brain hematomas corresponded to what would be expected from gradual enlargement of the lesions. Fisher commented "When hemorrhage occurs when the patient is under observation, it will be found that the deficit comes not instantaneously but gradually and steadily over an appreciable length of time, possibly 10 minutes or a few hours or even a few days."[68] Before Fisher, most authors described sudden onset, maximal at onset symptoms and signs. Fisher also analyzed the clinical findings in patients with hematomas found at the common sites for hypertensive ICH – putamen, thalamus, pons, and cerebellum. Recall that Fisher's contributions cited so far occurred "B.C." (i.e., before CT scans). Hematomas could only be diagnosed at that time if corroborated at necropsy or if they caused blood in the spinal fluid or mass effect on cerebral angiography. Only the larger hematomas were diagnosed, so that the clinical findings described by Fisher applied only to larger hematomas.

The advent of computed tomography (CT) scanning into clinical neurology in the 1970s helped greatly expand knowledge about ICH. CT proved to be a nearly ideal technology for the diagnosis of brain hemorrhage. Hematomas appeared as white hyperdense lesions, in stark contrast to adjacent tissues which were various shades of gray. The location, size, shape, drainage into the ventricular system, or surface cerebrospinal fluid were all readily visible on CT.[70] CT also showed surrounding edema, pressure effects on adjacent structures, and shifts and herniations caused by the hematoma and local mass effects.[70,71] The introduction of magnetic resonance imaging (MRI) in the 1980s helped in the detection of old hemosiderin-containing cavities and also recognition of vascular malformations. MRI also allowed visualization of the hematomas in various imaging planes so that 3-dimensional reconstruction of the exact locations and dimensions was now possible.

The capability of diagnosing brain hemorrhage safely and with certainty during life was a great advance. Prior ideas, concepts, and teachings about ICH had been based on series of patients studied at necropsy. Clinicopathological series were heavily biased toward larger hematomas that led to death. Now clinical–CT correlation led to recognition of the findings in patients with small and moderate-sized lesions that probably could not have been reliably diagnosed before CT. Clearly, neuroimaging using CT and MRI led to revision of concepts about ICH. Headache, vomiting, and reduced consciousness were features of large hematomas but were often absent in patients with smaller lesions. New predilection sites for hematomas were noted, especially the caudate nucleus[72,73] and the cerebral lobar white matter.[74,75]

Most important, the clinical findings described by Gowers, Osler, and Fisher applied to the larger hematomas at each site of predilection; the findings in patients with hematomas at each of the sites included a spectrum of abnormalities depending on the location and size of the artery involved. The penetrating arteries, including the medial and lateral lenticulostriate arteries, thalamogeniculate arteries, thalamoperforating arteries, recurrent artery of Heubner, and paramedian pontine arteries, are not single vessels but fans of parallel arteries of different size. For example, basal ganglionic hematomas can arise medially from small medial lenticulostriate arteries or far laterally from lateral lenticulostriate artery branches to the lateral putamen–external capsule region. Some hematomas are small and involve the anterior limb of the internal capsule. Larger lesions usually involve the putamen and the genu and anterior portion of the posterior limb of the internal capsule, and some hematomas involve the posterior portion of the putamen and the far posterior limb of the internal capsule, sometimes extending laterally into the temporal lobe isthmus and temporoparietal white matter.[76,77] Clinical findings vary at each site described. Anterior lesions usually have relatively minor paralysis with good recovery of function. Middle lesions are the largest and patients have the poorest prognosis for recovery from hemiplegia. Posterior lesions often have hemisensory signs and aphasia (if left brain), and little if any paralysis.[76,77] Similarly, thalamic hematomas conform to the recognized arterial territories of arteries supplying the thalamus. Anterior

and anterolateral thalamic hematomas are fed by the polar (tuberothalamic) artery; ventrolateral thalamic hematomas are supplied by thalamogeniculate artery branches; posteromedial thalamic hematomas are supplied by thalamic-hypothalamic (thalamoperforating) arteries; and dorsal and pulvinar thalamic hemorrhages are supplied by posterior choroidal artery branches.[77,78] Fisher had described the usual findings in patients with large, usually ventrolateral and posteromedial thalamic hematomas. The clinical signs are quite different at each of these thalamic sites, and also depend on size, spread, and drainage pattern.[77,78] Similarly, the syndromes of pontine, midbrain, and cerebellar hemorrhage vary with the vessel involved. The topic of the general history of ICH is covered in more depth elsewhere.[77]

The modern era (1975–present)

An explosive growth of interest and knowledge about stroke occurred during the last quarter of the twentieth century. Advances in technology allowed doctors to better image the brain and its vascular supply safely and quickly during life. Databases and registries of large numbers of well-studied stroke patients helped identify and quantify the most common clinical, imaging, and laboratory findings in patients with various stroke syndromes. Epidemiological studies identified more accurately the risk factors for stroke-prevention strategies. New surgical and medical treatments were introduced. Therapeutic trials began to evaluate systematically the efficacy and safety of some of these treatments. Physicians began to explore the use of devices that could be introduced through the arterial system to treat various lesions. Thrombolysis became a reality and strokes were considered a medical emergency requiring urgent attention. Stroke units were formed in many hospitals and greatly improved the care of stroke patients.

Advances in diagnostic technology

Hounsfield of the research laboratories of Electric Musical Instruments (EMI) in Britain originated the concept of computed tomography (CT) during the mid-1960s. The instrument was first tried at the Atkinson-Morley Hospital in London.[79] CT scanners were first introduced to North America in 1973. Films from first-generation scanners were very primitive, but by the late 1970s, third-generation scanners had made CT a useful, diagnostic technique. By the mid-1980s, CT was readily available throughout North America and most of Europe. The advent of MRI into clinical medicine in the mid-1980s was a further major advance. MRI proved superior to CT in showing old hemosiderin-containing hemorrhages and in imaging vascular malformations, lesions abutting on bony surfaces, and posterior fossa structures. MRI also made it easier to visualize lesions in different planes by providing sagittal, coronal, and horizontal sections. Improved filming techniques have made it possible to image the brain vasculature through the techniques of magnetic resonance angiography and CT angiography. Diffusion-weighted MRI (DWI) films made it possible to show infarcts soon after ischemia onset. Diffusion tensor imaging (DTI) made it possible to analyze white matter tracts.

Ultrasound was introduced to medicine in 1961 by Franklin and colleagues, who used Doppler shifts of ultrasound to study blood flow in canine blood vessels.[79] B-mode ultrasound was soon used to provide images of the extracranial carotid arteries noninvasively. By the early 1980s, B-mode, continuous-wave, and pulsed-Doppler technology could reliably detect severe extracranial vascular occlusive disease in the carotid and vertebral arteries in the neck. Sequential ultrasound studies allowed physicians to study the natural history of the development and progression of these occlusive lesions and to correlate the occurrence and severity of disease with stroke risk factors, symptoms, and treatment. In 1982, Aaslid and colleagues introduced a high-energy bidirectional pulsed-Doppler system that used low frequencies to study intracranial arteries, termed transcranial Doppler ultrasound (TCD).[80] TCD made possible noninvasive detection of severe occlusive disease in the major intracranial arteries during life, as well as sequential study of these lesions.

Introduction of echocardiography and ambulatory cardiac rhythm monitoring in the 1970s and 1980s greatly improved cardiac diagnoses and detection of cardiac sources of embolism. By the early 1990s, clinicians could safely define the nature, extent, and localization of most important brain, cardiac, and vascular lesions in stroke patients. By the end of the twentieth century, advanced brain imaging with CT, MRI, and newer magnetic resonance (MR) modalities, including fluid attenuating inversion recovery (FLAIR) images, diffusion, perfusion, and functional MRI, and MR spectroscopy, were able to show clinicians the localization, severity, and potential reversibility of brain ischemia. Vascular lesions could be quickly and safely defined using CT angiography, MR angiography, and extracranial and transcranial ultrasound. Cardiac and aortic sources of stroke were studied using transesophageal echocardiography. Advanced hematological testing led to new insights into the role of altered coagulability in causing or contributing to thromboembolism. Clinicians were finally able to recognize and quantify quickly and accurately the key data elements needed to logically treat patients with brain ischemia and hemorrhage.

Stroke data banks and registries

During the middle years of the twentieth century, clinicians described clinical phenomenology by personally studying and describing small groups of patients. During the 1970s and 1980s, the diagnostic technological advances made it possible to define the clinical and laboratory features of nonfatal, even minor, strokes and prestroke vascular lesions. With better knowledge of clinical and imaging features, clinicians naturally sought more quantitative data. How often did intracerebral hemorrhages or lacunar infarcts occur? How often did each of the clinical symptoms and signs occur in each subtype of stroke? Clinicians recognized that valid, statistically meaningful data could not be collected unless large numbers of patients with a wide spectrum of representative cases were studied and analyzed. The advent of computers in medicine in the 1970s greatly facilitated the storage and analysis of large quantities of complex data. Collection of data on large numbers