# 1

# A History of Cerebrovascular Disease since the Renaissance

*James F. Toole, MD*

> Those who cannot remember the past are condemned to repeat it.
>
> George Santayana

In the last three decades, there have been tremendous advances in technology and scientific knowledge that have revolutionized stroke prevention, diagnosis, and treatment. Noninvasive, painless, and safe imaging techniques now enable the clinician to pinpoint the size and location of brain lesions that in the not too distant past could be suspected but not easily or safely confirmed. Only 40 years ago, for example, the standard mode for differentiating brain hemorrhage from ischemic infarction was a lumbar puncture to examine for blood in the cerebrospinal fluid, and later a midline echogram might have been utilized to detect a shift of the midline structures caused by a unilateral cerebral lesion. Both of these techniques have been rendered obsolete by computed cranial tomography and magnetic resonance imaging studies. Similarly, therapeutics have improved dramatically. Clinical trials have better defined the usefulness of older drugs such as aspirin and anticoagulants, and tissue plasminogen activator (tPA) has emerged as a means to dissolve a clot and reestablish blood flow quickly enough to prevent brain tissue destruction.

In addition to these and other advances in diagnosis and treatment, infrastructural improvements in health care delivery, research collaboration and funding, and dissemination of information have spurred progress. Local, regional, national, and international health systems have been created for patients suffering with stroke. Responsibility for the care of individuals with stroke has shifted from individual physicians to specialized stroke treatment and rehabilitation teams that improve the outcome. Emergency therapies require knowledgeable health professionals to be available at all times. Large-scale public funding of biomedical research has enabled large multicenter clinical trials to provide data that increasingly dictate the treatment. Electronic editing and publishing have revolutionized medical research, communication, and clinical practice, in the process reducing costs and increasing the availability of information regarding effective therapy.

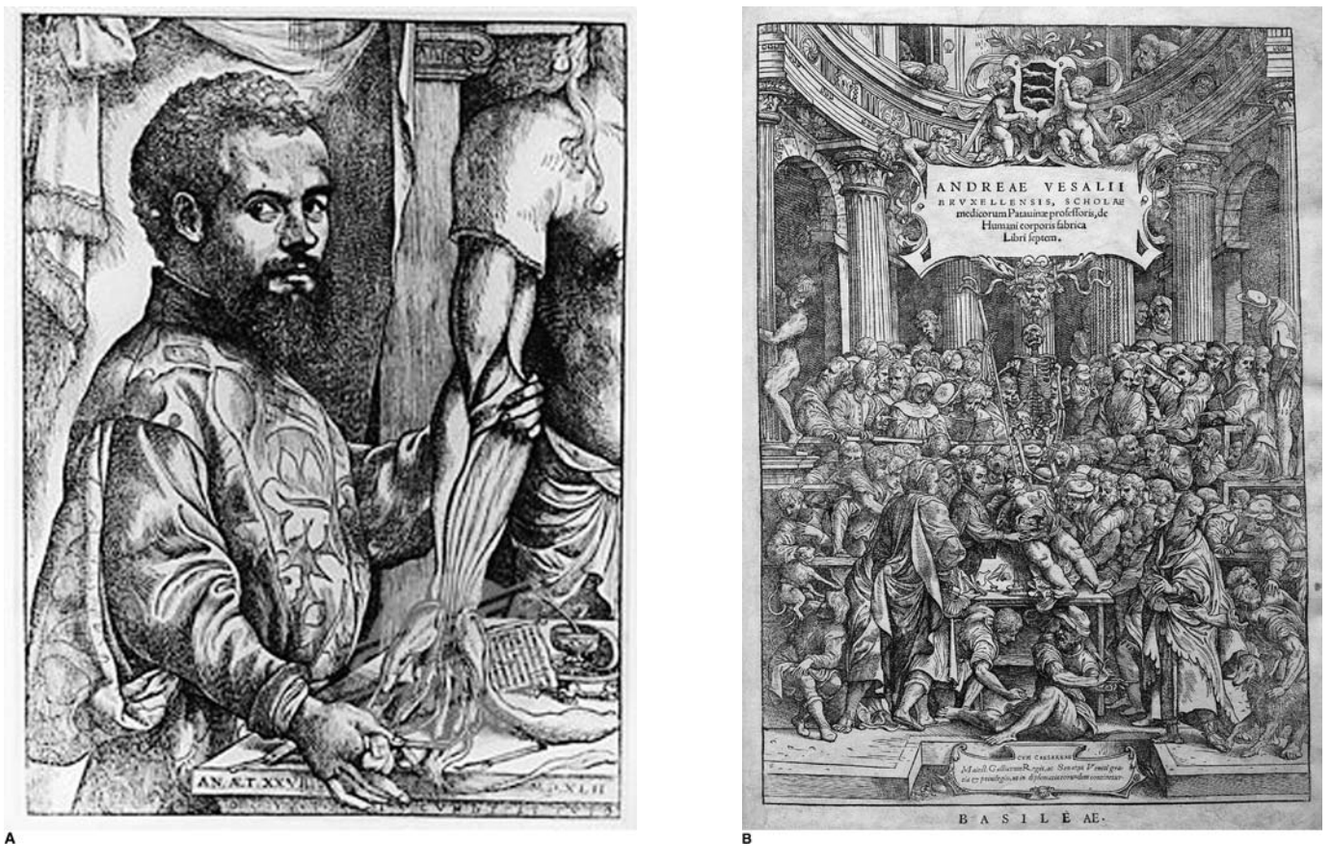
Knowledge of stroke rests on the generations of accumulated facts and observations that underpin our understanding of the pathophysiology of cerebrovascular disease. The threads of this long process are woven subtly into the fabric of our knowledge as eponymic names of signs and diseases and as long-accepted assumptions. But without a sense of the historical continuity of ideas, it is difficult to understand them. Therefore, we highlight some of the milestones in our understanding of cerebrovascular disease, concentrating on the post-Renaissance era.

## OBSERVATIONAL STUDIES OF ANATOMY AND PATHOPHYSIOLOGY

Knowledge of human anatomy, and therefore understanding of function, were impeded during the Middle Ages when dissection of the human body was forbidden because resurrection of the body was an act of faith. Nevertheless, dissections were performed secretly in Bologna by Mondino di Luzi in the fourteenth century.[1] William Harvey, in England, is thought to have dissected the bodies of his own father and sister. Andreas Vesalius revolutionized the study of anatomy with the publication of his *De Humani Corporis Fabrica* (Figure 1-1), challenging the centuries-old teachings of Galen with new observations based on his human dissections.[2] Vesalius's pupil Fallopius illustrated the cerebral blood vessels in his *Observationes Anatomica* (1561) and included a description of the circle of Willis. However, it took many years for these early concepts of blood circulation to be reexamined and validated by Harvey[3] and accepted by others such as Wepfer, Lower, and Willis (Figure 1-2).[4–6]

Efforts toward prevention and therapy were scant because stroke was attributed to punishment by God, who "smote, or struck down" sinners, thus the origin of the term stroke. The first monographs on apoplexy were published by Gregor Nymmann from Wittenberg, Germany, in 1619 and Johann Jakob Wepfer working in Germany and Switzerland in 1658.[5,7] Wepfer was the first to record that stroke can be caused by hemorrhage as well as by clotting.

In 1658 Wepfer described "corpora fibrosa" in the wall of blood vessels as the cause for vascular stenosis and stroke




A B

Figure 1-1. A: Andreas Vesalius. B: Illustration from Vesalius, *De Humani Corporis Fabrica* (1543).

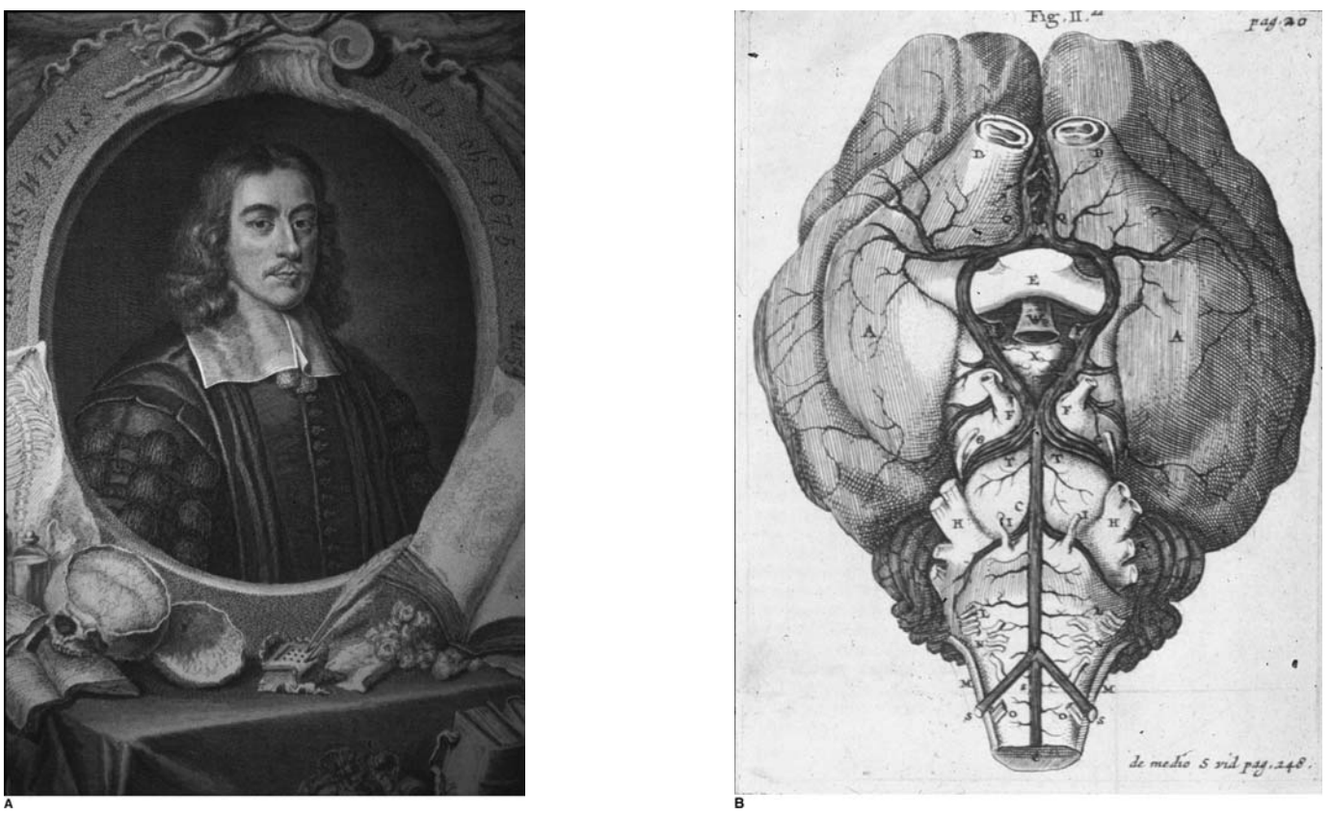



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Figure 1-2. A: Thomas Willis. B: The circle of Willis as depicted in the Samuel Pordage English translation of Willis's *Cerebri Anatome* (1681).

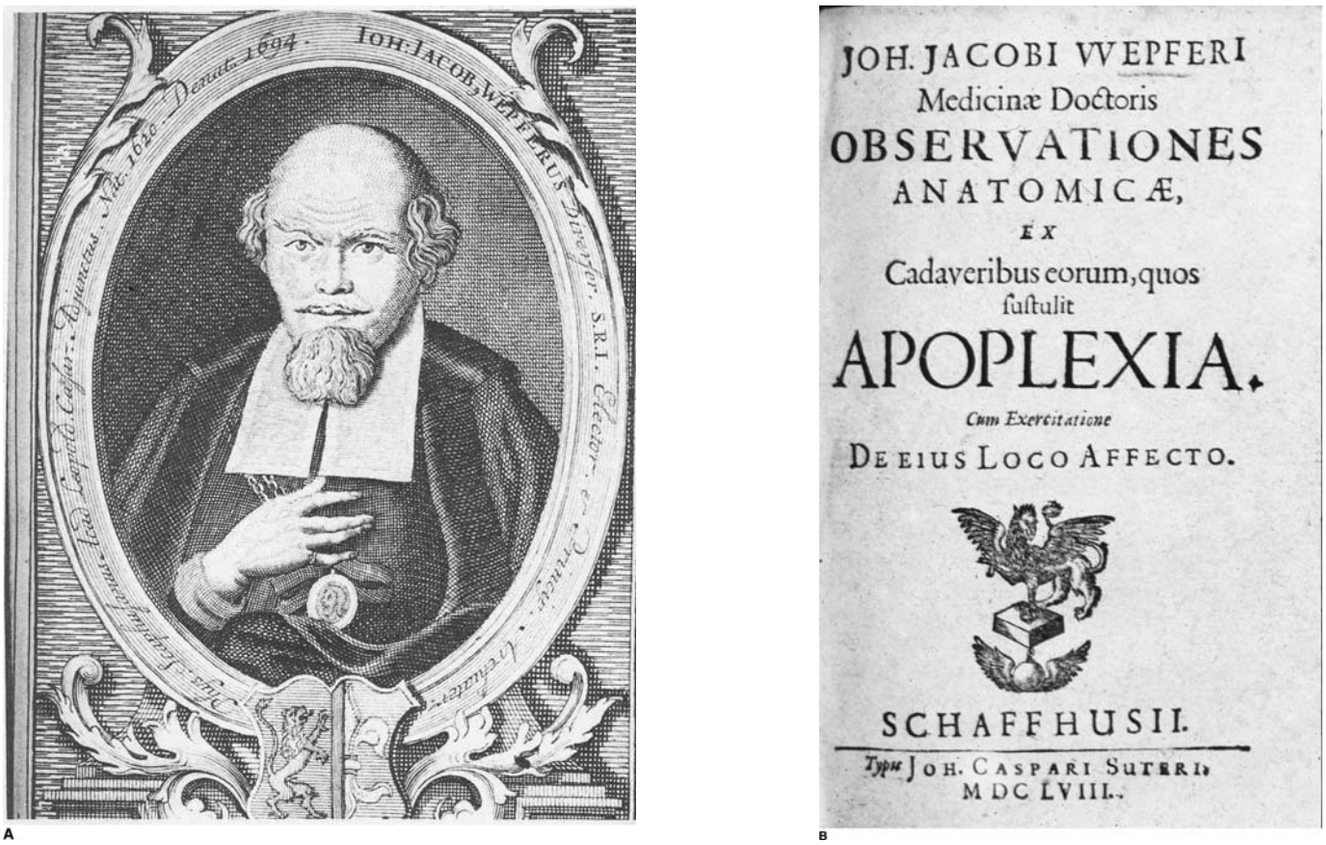



Figure 1-3. A: Johann Jacobus Wepfer. B: Title page from Wepfer's *Apoplexia* (1658).

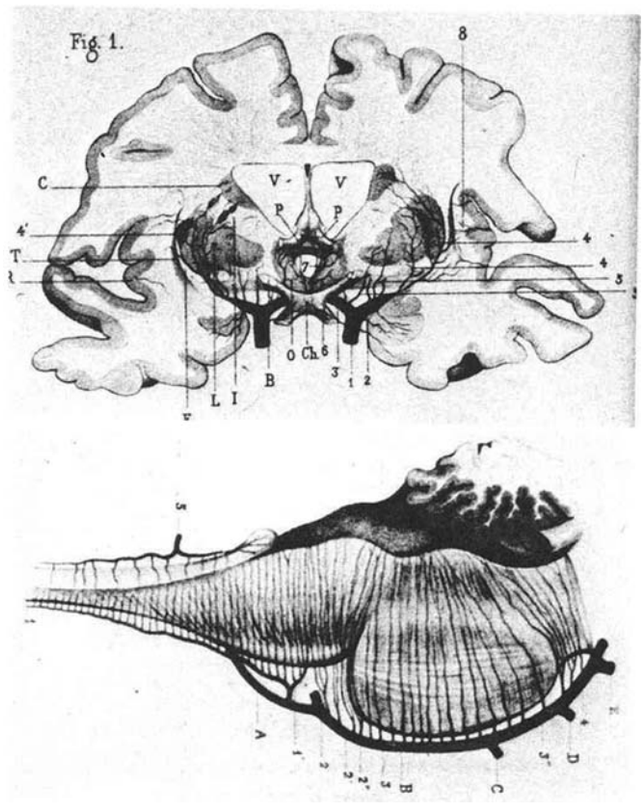



Figure 1-4. Duret's 1874 drawings of the distribution of the lenticulo-striate arteries and the penetrating branches of the basilar artery.

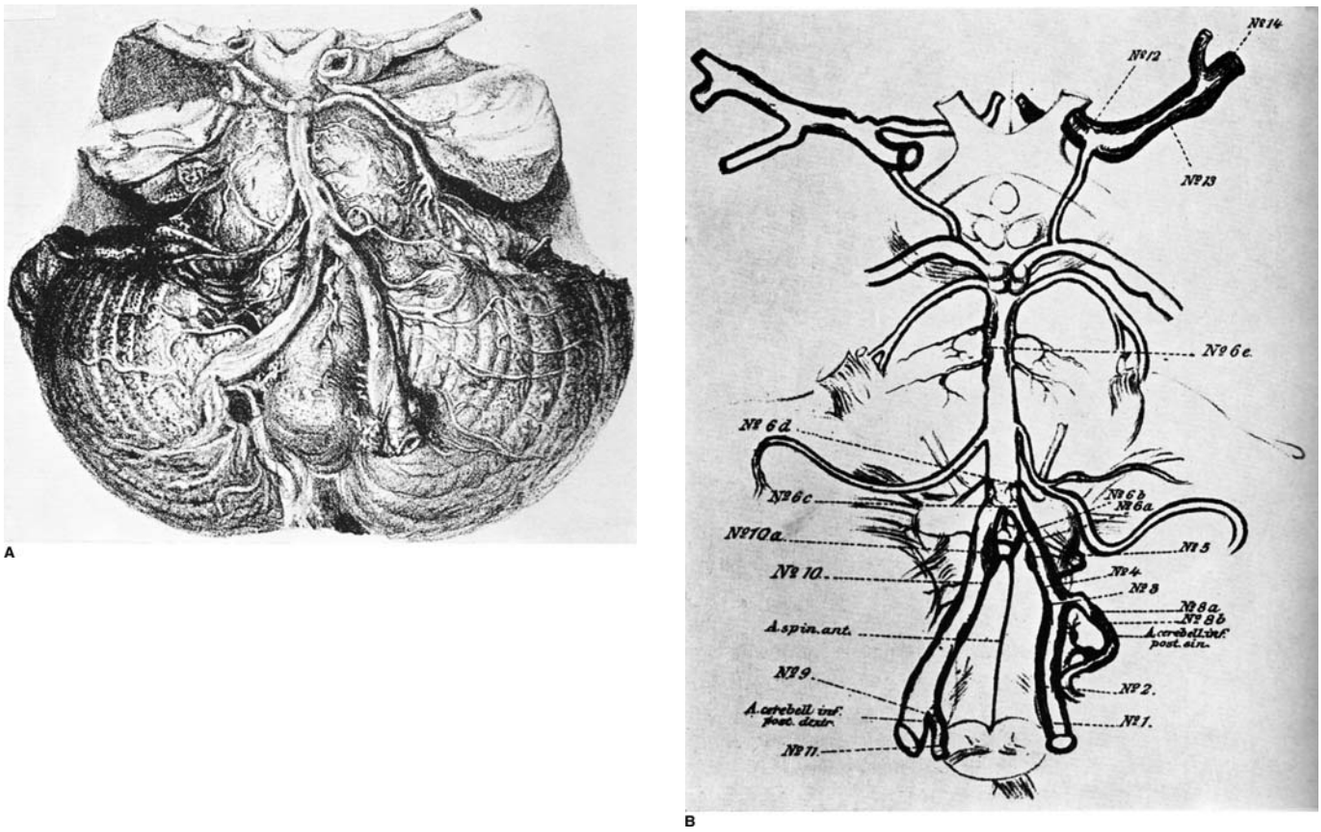



Figure 1-5. A: Autopsy drawing of Wallenberg's patient showing atherosclerosis of the major cerebral arteries. B: Another drawing illustrates the occlusion of the posterior inferior cerebral artery.

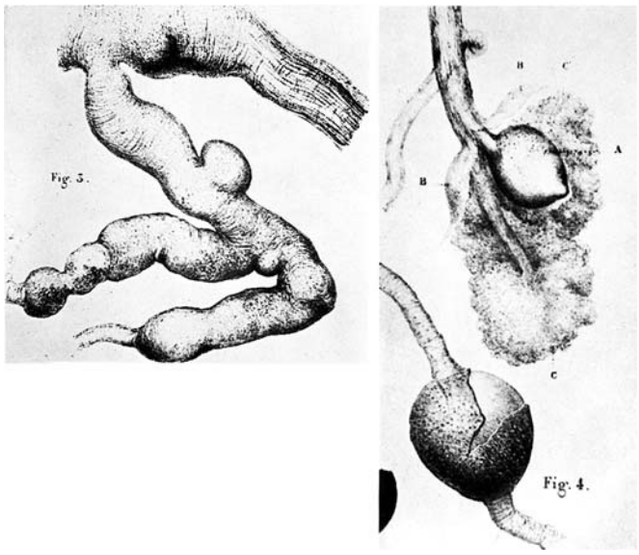
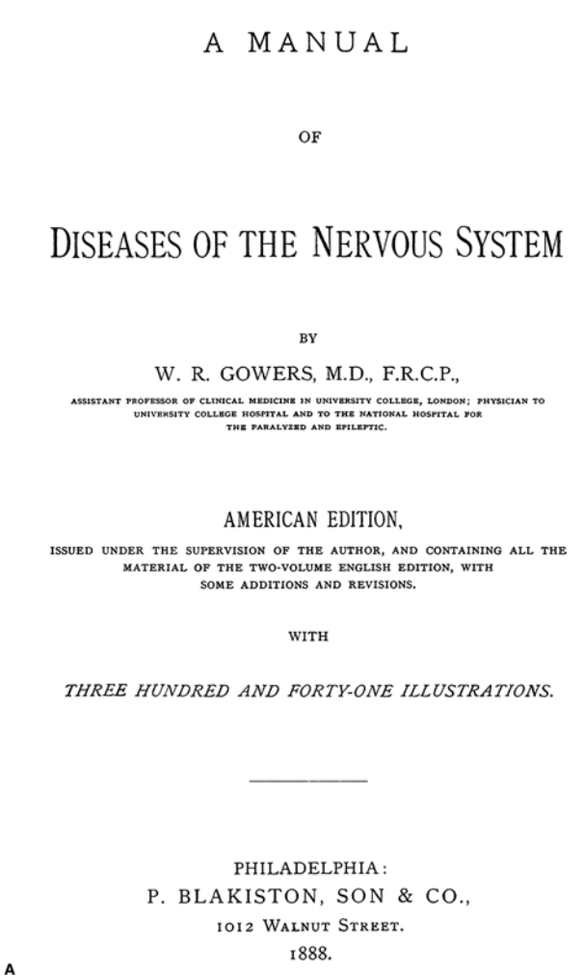



Figure 1-6. Bouchard's 1822 drawings of miliary aneurysms, lesions that he and Charcot believed to be the source of bleeding in intracranial hemorrhage.

(Figure 1-3).[5] Later, Bayle postulated that calcified carotid artery plaques could lead to stroke.[8] However, localization of cerebral function and the delineation of perfusion territories did not gain momentum until the eighteenth century. In 1754 von Swieten in his commentaries on Boerhaave's work stated that stroke could be caused by an embolism from the heart.[9] Morgagni of Padua correlated different clinical stroke types with postmortem studies in his monumental work *De Sebidus.*[10,11]



A MANUAL

OF

DISEASES OF THE NERVOUS SYSTEM

BY

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AMERICAN EDITION,

ISSUED UNDER THE SUPERVISION OF THE AUTHOR, AND CONTAINING ALL THE MATERIAL OF THE TWO-VOLUME ENGLISH EDITION, WITH SOME ADDITIONS AND REVISIONS.

WITH

*THREE HUNDRED AND FORTY-ONE ILLUSTRATIONS.*

PHILADELPHIA:
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1012 WALNUT STREET.
1888.

A

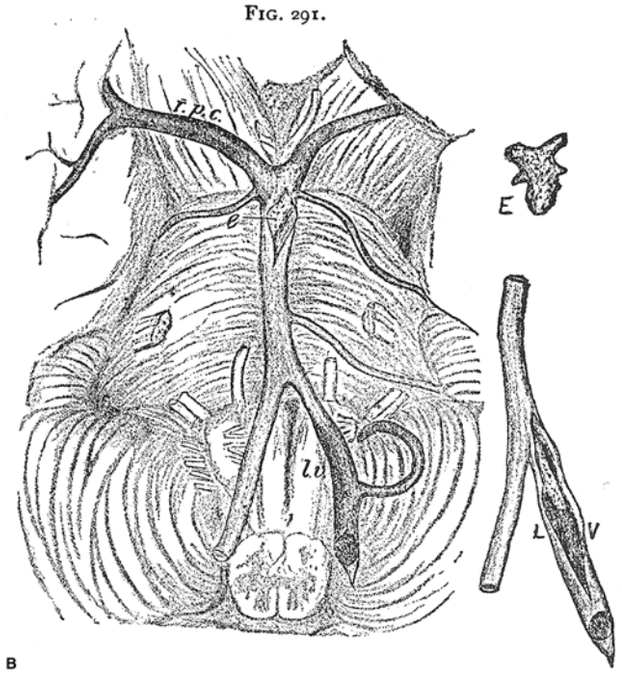


FIG. 291.

B

Figure 1-7. A: Title page of Gowers's *Manual of Diseases of the Nervous System*, the monograph that was sometimes called the "Bible of Neurology." B: Drawing of a vertebral artery embolism from Gowers's *Manual*.

The foundation for modern topography and classification of stroke was laid in the 1800s by the work of many individuals, including Abercrombie in Edinburgh, Carswell and Bright in London, and Heubner in Leipzig.[12–15] Additional contributions were made by Virchow and by Cohnheim[16,17] as well as by Charcot, Cruveilhier, Duret, and Foix in France.[16,18–21] Duret in 1873 was one of the first to delineate vascular territories (Figure 1-4), and numerous eponymic syndromes based on brainstem vascular occlusions (Figure 1-5) were described.[22–24] Charcot and others described anatomical variations, and Bouchard described dilations of the small penetrating arteries that they believed were responsible for brain hemorrhage (Figure 1-6).[21,25]

During the early to mid-nineteenth century, hemorrhagic and nonischemic stroke were differentiated by Carswell, Cruveilhier, Durand-Fardel, and many others.[14,19,26] Chiari in 1905 and Ramsay Hunt in 1914 established that cerebral vascular disease occurs at the carotid bifurcation in the neck.[27,28] They suggested that the carotid arteries should be examined clinically, an idea that was later made feasible by the introduction of cerebral angiography during the 1920s, ultrasound in the 1960s, and magnetic resonance angiography and cranial computed tomography (CT) angiography more recently.

Gowers in 1885 described cardiac embolism and thrombosis as an etiology of stroke (Figure 1-7).[29,30] This concept was later emphasized by Osler and McCrae in the neurological diseases portion of their influential *Modern Medicine – Its Theory and Practice.*[31] During the early twentieth century, it became obvious that atrial fibrillation could cause cerebral infarction, and in the 1990s warfarin was shown to reduce the risk of embolic stroke due to cardiac embolism. Warfarin was introduced for anticoagulation in humans in 1954.

In 1933 Wolkoff undertook the scientific study of cerebral arteriosclerosis, and Keele noted the effects of systemic hypertension on the carotid sinus region.[32,33] More recent contributions to stroke categorization were made by Zülch in Germany and C. Miller Fisher in the United States.[34–37] Until the 1950s the cause of carotid thrombosis was debated, with several authors suggesting syphilis or trauma as the etiology. In 1951, Fisher and Adams established that carotid artery atherosclerosis can cause cerebral infarction, often preceded by a transient ischemic attack due to embolic particles from an atherosclerotic plaque.[38] In 1961 Toole and colleagues presented two patients with stenosis of the left subclavian artery causing reversal of flow through the vertebral artery into the arm, introducing the concept of the subclavian steal syndrome.[39]

## CEREBRAL PERFUSION, METABOLISM, AND NEUROIMAGING

In 1762 von Haller observed that the caliber of pial vessels changed during the cardiac cycle.[40] By 1783 Monro and Kellie in Scotland had formulated the doctrine named for them that the blood volume within the nonexpandable skull cavity tends to remain constant at all times.[41] However, Burrows showed in his 1846 monograph that the blood volume within the brain can vary somewhat with changing physiological states.[42] In 1850 Donders of Utrecht observed the response of pial vessels to asphyxia through a glass window in the skull.[43] Thereafter, Sherrington and Roy introduced the modern concept of cerebral vascular autoregulation.[44] Based partly on their demonstration of autoregulation of cerebral blood flow, Kety and Schmidt as well as McHenry developed methods to measure regional cerebral blood flow in patients using inert gases such as krypton and xenon.[45–49]

Imaging of arteries and veins using blood-borne radiopaque media and X-rays was introduced by Egas Moniz in Portugal.[50] He initially injected strontium bromide as an intra-arterial contrast agent but later substituted iodinated contrast.[51] He was awarded the Nobel Prize – for his role in developing the now-discredited prefrontal leucotomy rather than his more long-lasting contribution to the diagnosis of vascular disease.[52] In 1961 Sokoloff initiated functional brain imaging by demonstrating the relation between regional cerebral blood flow and brain metabolism.[53,54] The use of single photon emission computed tomography (SPECT) for assessment of stroke patients today owes a debt to the first nuclide images by Kuhl and Edwards in 1963.[55]

The once critical bedside examination skills for localizing a brain lesion have been to some extent supplanted by the revolution in neuroimaging, especially computed cranial tomography in the 1970s and magnetic resonance imaging (MRI) in the 1980s. The construction of the first prototype camera based on the Compton effect, suggested in 1977, was performed by Singh and Doria in 1983.[56,57] The development of SPECT, xenon CT, positron emission tomography (PET), and functional MRI during the last three decades augment the ever-growing array of imaging techniques available for diagnosis and targeted treatment of stroke patients today.

Noninvasive visualization of anatomy of the brain became possible with the development of head CT by Oldendorf and then by Hounsfield and Cormack of Britain during the 1970s.[58–60] Subsequently, MRI was developed during the 1980s by Mansfield in Britain and by Lauterbur in the United States, who were awarded the Nobel Prize in 2003.[61,62] MRI was based on the magnetic resonance phenomenon independently characterized by the U.S. physicists Bloch and Purcell, both of whom received the Nobel Prize in physics in 1952.[63–65] Continued advances in computer technology and data analysis techniques have reduced the image acquisition time and created new avenues for acute stroke diagnosis and treatment. The development of CT angiography and MR angiography during the 1980s and the improvement of these techniques during subsequent years now allow rapid, precise visualization of the brain and its vasculature.

The subsequent initial application of Doppler techniques for blood vessel assessment by Olinger in 1969 and by Reid and Spencer in 1972 was quickly followed by the application of ultrasound to depict the brain's blood supply.[66,67] Olinger, based on previous work by Herz and Bliss, described the visualization of carotid arteries by B-mode ultrasound imaging.[66,68] In 1972 Blue and colleagues demonstrated the diagnostic validity of B-mode ultrasound images by comparing them to conventional carotid arteriography.[69] Miyazaki and Kato furthered transcranial Doppler as a diagnostic tool for stroke patients by recording changes in blood flow velocities through the intact human skull based on the Doppler effect.[70]

## STROKE PREVENTION AND INTERVENTION

Identification of stroke risk factors provides a way to reduce the incidence of stroke by modifying the underlying condition or designing treatments based on specific pathophysiology. Recognition of the importance of tobacco use and systemic hypertension in the pathophysiology of cardiac disease and stroke led to more aggressive attempts to control them by education, diet, and medication, efforts that probably contributed to the decline in stroke incidence in recent years.[71]

The bark of the willow tree was used as a traditional herbal treatment for fever and pain in Europe long before its active ingredient acetylsalicylic acid (aspirin) was synthesized by chemists at the Bayer Company in Germany in 1887. In the 1960s the antithrombotic effect of aspirin was recognized, and the drug was introduced for the prevention of stroke in the 1970s.[72] Subsequent large-scale clinical trials showed that regular aspirin use reduced the risk of stroke due to atherosclerosis. Similarly, randomized clinical trials in the 1990s confirmed that warfarin, first introduced as an anticoagulant in humans in 1954, lowers the risk of ischemic stroke caused by cardiac embolism secondary to atrial fibrillation.

After 40 years of intense research, tPA (tissue plasminogen activator) was introduced in 1995 and became standard treatment for acute ischemic stroke for individuals presenting within 3 to 4.5 hours of symptom onset. However, the first randomized trial investigating the feasibility of a thrombolytic drug was published in 1963.[73] Further trials between 1963 and 1993 using tPA, urokinase, and streptokinase were inconclusive regarding the effectiveness and safety of thrombolytic drugs.[74–76] Neuroimaging techniques were incorporated into the multicenter acute stroke trial designs of the 1990s that demonstrated the feasibility of intravenous tPA administration in acute stroke patients, leading to the pivotal study of tPA by the National Institute of Neurological Disorders and Stroke (NINDS) in 1995 and FDA approval in 1996.[77,78]

## SURGICAL AND INTRAVASCULAR THERAPIES

Before the use of carotid endarterectomy to prevent stroke from carotid atherosclerosis, carotid artery surgery was occasionally performed for other reasons, although often unsuccessfully.[79,80] Ligation of the common carotid artery without causing neurological deficit was documented in an aneurysm patient by Hebenstreit in 1793.[81] During the early twentieth century, carotid artery compression tests were explored and several initial carotid artery surgery efforts were recorded.[82,83] In 1916 Parczewski removed an arteriovenous aneurysm in the common carotid artery and performed a successful end-to-end anastomosis.[84] Carotid ligation was also an early means for controlling a distal carotid aneurysm.[85] In 1950 Gordon-Murray in Toronto restored the circulation to the common carotid artery of a 54-year-old man with syphilitic aortitis and occlusion of all four major cervicocephalic arteries.[83] The following year in

**Table 1-1: Stroke Milestones**

| *Discovery* | *Location* | *Person* | *Year* |
|---|---|---|---|
| *De Humani Corporis Fabrica*, first drawings of cerebral circulation | Italy | Vesalius | 1543 |
| Depiction of circle of Willis | Italy | Fabricus | 1561 |
| Characterization of blood circulation and heart motion | UK | Harvey | 1628 |
| Description of physiological role of circle of Willis and described TIAs | UK | Willis | 1621–1675 |
| *Syntagma Anatomicum*, illustration of the complete circle of Willis | Germany | Vesling | 1647 |
| First monographs published on apoplexy | Germany, Switzerland | Wepfer | 1619–1657 |
| Description of atherosclerosis | Germany | Wepfer | 1658 |
| Arteries as etiology for stroke, describes calcified plaques | France | Bayle | 1677 |
| Apoplexy caused by cardiac embolism | Netherlands | von Swieten | 1754 |
| Four volumes on apoplexy | Italy | Morgagni | 1761 |
| Monro-Kellie doctrine | Scotland | Monro and Kellie | 1783 |
| Further description of TIAs | UK | Heberden | 1802 |
| *Treatise on Apoplexy* with first illustration of SAH, first to identify anemia as a cause of stroke | Ireland | Cheyne | 1812 |
| *Pathological and Practical Researches on Disease of the Brain and Spinal Cord* | UK | Abercrombie | 1828 |
| Observation of pial vessels via sealed glass window in closed skull; description of Takayasu arteritis case | Netherlands | Donders | 1850 |
| Description of carotid thrombosis causing blindness, studies on emboli, ICH | Germany | Virchow | 1856 |
| Mapping vascular territories | France | Duret and Charcot | 1873–1874 |
| Cerebral vascular autoregulation | UK | Sherrington and Roy | 1890 |
| *Diseases of the Nervous System*, ICH, aneurysms, cerebral emboli | Canada | Osler | 1893 |
| Discovery of X-rays | Germany | Roentgen | 1895 |
| Histopathology of arteriosclerosis, describes Alzheimer disease | Germany | Alzheimer | 1897 |
| Established that extracranial vascular disease leads to stroke | Italy | Chiari | 1905 |
| First description of carotid occlusion causing stroke | USA | Hunt | 1914 |
| Concept of hypertensive encephalopathy, chronic white matter disease | Germany | Binswanger | 1917 |
| Pneumo-encephalography | USA | Dandy | 1918 |
| Cerebral angiography description | Portugal | Moniz | 1927 |
| Catheter angiography, awarded 1956 Nobel Prize | Germany | Forssmann | 1928 |
| Scientific study of cerebral arteriosclerosis | Sweden | Wolkoff | 1933 |
| Plethysmography to measure CBF in humans | USA | Ferris | 1941 |
| Determination of human CBF and oxygen consumption | USA | Kety and Schmidt | 1948 |
| Cutaneous method for inserting arterial catheter | Sweden | Seldinger | 1953 |
| Carotid artery surgery | UK | Eastcott, Pickering, and Rob | 1953 |
| First Princeton Conference on cerebrovascular disease | USA | Wright | 1954 |
| Prospective Randomized Study of carotid endarterectomy | USA | DeBakey | 1959 |

*(continued)*

**Table 1-1** *(continued)*

| *Discovery* | *Location* | *Person* | *Year* |
|---|---|---|---|
| Demonstration of increased rCBF with brain activity | USA | Sokoloff | 1961 |
| Quantitative measurement of rCBF in humans | Sweden | Ingvar and Lassen | 1961 |
| Reversal of flow in vertebral artery named subclavian steal | USA | Toole | 1961 |
| Tomographic brain images with SPECT | USA | Kuhl and Edwards | 1963 |
| Visualization of carotid arteries by B-mode ultrasound | USA | Olinger | 1969 |
| Ultrasound images of interior of blood vessels | USA | Reid and Spencer | 1972 |
| B-mode ultrasound scanning and results correlated with conventional arteriography | USA | Blue, McKinney, and Barnes | 1972 |
| Computerized cranial tomography | UK | Hounsfield, Ambrose, and Cormack | 1973 |
| SPECT | USA | Everett et al. | 1977 |
| Prototype of Compton camera built for SPECT | UK | Singh and Doria | 1983 |
| MRA imaging of arteries | USA | Dumoulin et al. | 1987 |
| Anticoagulation is proven effective for stroke prevention in atrial fibrillation, stroke centers introduced, tPA introduced, ACAS | USA | | 1970s–2000 |
| NASCET and ACAS trials result in evidence-based indication for carotid endarterectomy | USA and Canada | | 1990s |
| fMRI developed for brain mapping | USA | Ogawa and Lee | 1993 |
| Nobel Prize for Medicine for MRI | USA | Mansfield and Lauterbur | 2003 |
| International Stroke Society, World Stroke Federation, and individual countries form societies for dissemination of knowledge through internet | Worldwide | | 2000–present |

ACAS = Asymptomatic Carotid Atherosclerosis Study; CBF = cerebral blood flow; fMRI = functional magnetic resonance imaging; ICH = intracerebral hemorrhage; MRI = magnetic resonance imaging; NASCET = North American Symptomatic Carotid Endarterectomy Trial; rCBF = regional cerebral blood flow; SPECT = single photon emission computed tomography; TIA = transient ischemic attack; tPA = tissue plasminogen activator.

Argentina, Carrea and colleagues surgically reconstructed the carotid artery, joining the external carotid artery to the proximal internal carotid artery to reperfuse the brain.[86]

Strully and colleagues described one of the first endarterectomy procedures in 1953, and, in 1954 Eastcott and associates successfully reconstructed the carotid artery in an individual with intermittent hemiplegia.[87,88] In 1975 Michael DeBakey published the results of a cooperative study to determine the efficacy for stroke prevention by comparing endarterectomy to usual medical management and treatment. This was one of the first multicenter international trials in stroke treatment. DeBakey noted in that article that his first carotid endarterectomy patient had undergone an endarterectomy in 1953 and had lived for 19 years before death from coronary artery disease.[89,90] With the recent advancement of neuroimaging and the introduction of new microcatheters, endovascular interventions have now become state-of-the-art and may replace invasive surgical approaches for carotid disease.[91]

The development of microcatheters, thrombolytic agents, and intravascular devices have made acute stroke treatment feasible. In the early 1960s the concept of percutaneous luminal angioplasty was introduced, and Charles Dotter was one of the first to publish a technique for placing endovascular stents via a percutaneous approach.[92] As cerebral angiography improved, more intricate intravascular treatment techniques became feasible. Luessenhop and colleagues demonstrated the feasibility of intracranial artery catherization with flow-directed balloon-tipped catheters in 1964.[93,94] Gruentzig, a Swiss radiologist, was the first to perform transluminal coronary angioplasty in 1977.[95] The further development of new stents during the 1980s allowed stent applications starting with the work of Maass and colleagues.[96] He was one of the pioneers to use the earliest generation of newly developed self-expanding spring coils for stenting of the iliac and inferior cava vein and the aorta at the University of Zurich in Switzerland. In the early 1970s Serbinenko initiated endovascular therapy, reporting the first treatment of an intracranial aneurysm

using a detachable balloon inserted via a newly developed microcatheter.[97,98] Stent development and catheter techniques evolved further during the 1970s and 1980s, first in the area of peripheral and coronary artery stenting and later in the treatment of cerebrovascular disease, allowing treatment of extra- and intracranial stenosis, vascular malformations, aneurysms, and the local injection of intra-arterial thrombolytics for acute ischemic stroke.

## EVIDENCE-BASED MEDICINE AND STROKE ORGANIZATIONS

In reviewing the development of the field of stroke over the centuries it becomes apparent how much of our knowledge represents global interaction by physicians and scientists from many nations. The collaborative effort is demonstrated by the formation of national and international stroke societies, first in the United Kingdom in 1898, later in the United States, and now globally.

Research and care for patients with stroke and other neurologic illness in the United States was accelerated by the National Institutes of Health (NIH) and the National Institute of Neurologic Disease and Blindness (later the National Institute of Neurological Diseases and Stroke, or NINDS). At the end of World War II there were millions of veterans with neuropsychiatric disorders, accounting for an estimated 20% of patients in general hospitals. However, in 1950 there were relatively few neurologists, leading to a series of meetings and the identification of nervous system disorders as a national priority. The expansion of the NIH made possible the funding of the numerous large-scale, prospective multicenter clinical trials which have revolutionized our understanding of stroke in recent years. Many names are associated with this renaissance, but the most prominent are Drs. Richard L. Masland, Murray Goldstein, and Seymour Kety, who was appointed to oversee the internal research effort.[99] Ground-breaking clinical trials have studied the management of intracranial aneurysms, subarachnoid hemorrhage, carotid artery stenosis, transient ischemic attacks, hypertensive stroke, multiple infarct dementia, stroke due to sickle cell disease, and many other conditions.

Evidence-based medicine in neurology was introduced by the leadership of the Oxford Group with Sir Richard Doll and Richard Peto, who worked in synergy with new entrants to the neurosciences and neurology by designing, implementing, and reporting results of prospective randomized trials.

## CEREBROVASCULAR DISEASE IN CHILDREN

Although stroke occurs in children much less often than in the elderly, incidence figures suggest that childhood stroke is more prevalent than cerebral tumors and many other neurological problems, making stroke in children a major public health issue. For many years, however, the occurrence of cerebrovascular disease among childhood went largely unrecognized and unstudied.

Willis described a newborn who had a cerebellar hemorrhage, and Morgagni recorded a cerebral hemorrhage in a 14-year-old boy.[100] Few additional developments occurred in childhood stroke until the nineteenth century, when several series of children with stroke appeared, including reports by Osler in 1889 and an 1891 series of 594 children by Sigmund Freud and Oscar Rie.[101,102] In 1890 Sachs and Peterson emphasized that children with acquired hemiplegia have vascular dysfunction.[103] Ford and Schaffer systematically studied etiology and outcome in a series of 70 children with acquired hemiplegia, foreshadowing the modern approach to the diagnosis and management of stroke during gestation, infancy, and childhood.[104] After this auspicious beginning, the study of childhood cerebrovascular disorders languished for several decades until the late 1960s, when moyamoya disease was described in Japan.[105,106]

The development of CT and then MRI and magnetic resonance angiography made noninvasive confirmation of a stroke diagnosis feasible. Then Roach, Biller, and others began to emphasize the importance of cerebrovascular dysfunction among children.[107,108] In Canada deVeber and colleagues used a large ischemic stroke registry to study the clinical features, risk factors, and outcome of ischemic stroke in children. Transcranial Doppler techniques were developed by Robert Adams and colleagues to predict stroke risk due to sickle cell disease, and these methods have now been used to select high-risk individuals with sickle cell disease for several randomized clinical trials.[109] The story is still unfolding.[110]

## ADDITIONAL INFORMATION

Although our understanding of cerebrovascular disease has evolved at an uneven pace through the years, one can follow the threads of discovery through time, as concepts layer onto earlier ideas to form the foundation of what we now often take for granted. Knowing the pathway that we have followed adds depth and richness to of our understanding, but it is important to realize that our journey is far from finished. This brief overview is intended to highlight some of the major discoveries, hypotheses, and innovations (Table 1-1) that have stimulated the evolution of cerebrovascular disease as a discipline. For more details the reader is referred to the outstanding work on the history of neurology and stroke by McHenry, Garrison, Gurdjian, Fields, and Lemak.[111–114]

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