Part I General principles

Chapter 1

Introduction and perspective

Louis R Caplan

It was then that it happened. To my shock and incredulity, I could not speak. That is, I could utter nothing intelligible. All that would come from my lips was the sound ab which I repeated again and again ... Then as I watched it, the telephone handpiece slid slowly from my grasp, and I, in turn, slid slowly from my chair and landed on the floor behind the desk ... At 5:15 in that January dusk I had been a person; now at 6:45 I was a case. But I found it easy to accept my altered condition. I felt like a case.
Eric Hodgins[1]

"Cheshire Puss ... Would you tell me, please, which way I ought to go from here?"
"That depends a great deal on where you want to get to," said the Cat.
"I don't much care where –," said Alice.
"Then it doesn't matter which way you go," said the Cat.
"– so long as I get *somewhere*," Alice added ...
"Oh, you're sure to do that," said the Cat, "if you only walk long enough."
Lewis Carroll[2]

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.
William Osler[3]

Numbers

In the United States, according to 2014 statistics, 795 000 individuals have a stroke each year (610 000 are first strokes).[4] In 2010, one of every 19 deaths was attributed to stroke; on average a stroke occurred every 40 seconds and someone died of stroke about every 4 minutes. At any one time, there are approximately two million stroke survivors living in the United States. In China, approximately 1.5 million people die each year because of stroke.[5] Stroke affects three times as many women as breast cancer and yet receives much less public attention. For a long time, stroke has been the third leading cause of death in most countries in the world, surpassed as a killer only by heart disease and cancer. Strokes are an even more important cause of prolonged disability. Survivors of strokes are often unable to return to work or to assume their former effectiveness as spouses, parents, friends, and citizens. The economic, social, and psychological costs of stroke are enormous. In the United States, each ischemic stroke costs on average $140 000, and costs related to stroke nationwide was estimated to be $62.7 billion in 2007.[5]

Important medical and historical figures who had strokes

The history of the world has undoubtedly been altered by stroke. Many important leaders in science, medicine, and politics have had their productivity cut prematurely short by stroke. Marcello Malpighi, discoverer of capillaries and the microscopic anatomy of the lungs, kidneys, and spleen, died of an apoplectic right hemiplegia.[6] Louis Pasteur, at age 46 years, had a stroke that caused a left hemiparesis, although he continued to make important advances until additional strokes impaired his function at age 65.[6]

Three important figures in twentieth century neurology – Russell DeJong,[7] the first editor of the journal *Neurology*; Raymond Escourolle, the French neuropathologist; and H. Houston Merritt, longtime Columbia professor and writer of *Merritt's Neurology* –were severely disabled by multiple strokes in their later years. Two important political leaders during the early twentieth century, Vladimir Lenin and Woodrow Wilson, had intellectual impairment owing to stroke while they were at the helms of their countries at critical times in history. Lenin, at age 52 years, had the sudden onset of dysarthria and right hemiparesis. An observer noted that "often as he spoke, the words were slurred, and he paused several times like a man who has lost the thread of his argument."[8] Wilson, the architect of the League of Nations, had a series of small strokes that left him pseudobulbar and with a left hemiparesis at a time when he was ardently working for world peace and cooperation. The heads of state who met at Yalta and elsewhere to divide up the spheres of influence after the Second World War, Franklin D Roosevelt, Winston Churchill, and Joseph Stalin, (shown in Figure 1.1) all had severe cerebrovascular disease at the time.[8] Roosevelt subsequently died of a fatal stroke after years of severe hypertension.[9] History might have been different if the brains of these leaders had not been addled by strokes. Public awareness of stroke increased dramatically when President

Caplan's Stroke: A Clinical Approach, 5th Edition, ed. Louis R Caplan. Published by Cambridge University Press. © Cambridge University Press, 2016.

Figure 1.1 A photograph taken at the Yalta conference after the Second World War showing (from left to right in the front row) Winston Churchill, Franklin D Roosevelt, and Joseph Stalin. From Toole JF. *Cerebrovascular Disorders*, 4th ed. New York: Raven Press, 1990.

Dwight Eisenhower developed acute dysarthria, when Richard Nixon died after a large embolic cerebral hemisphere infarction, and when Ariel Sharon the Prime Minister of Israel was left unconscious after a series of cerebrovascular events.

The personal tragedy of stroke

The mortality, morbidity, and economic toll of stroke is impressive. Knowledge that government leaders may have brains damaged and even riddled with brain infarcts and hemorrhages is undoubtedly sobering. Yet even more important, in my own opinion, is the effect of stroke on the individual. What could be worse than the sudden inability to speak, move a limb, stand, walk, see, read, or feel, or become unable to understand spoken language, write, think clearly, or remember? Loss of function is often instantaneous and totally unanticipated; impairments may be transient or permanent, slight or devastating. The first common term for stroke, apoplexy, literally meant in Greek "struck suddenly with violence."[10] The word stroke refers to being suddenly stricken. Stroke patients tell graphically about the personal tragedy of their illness. Eric Hodgins, the popular author of *Mr. Blandings Builds His Dream House*, wrote an autobiographical account of his stroke that he titled *Episode*, from which I quoted at the beginning of this chapter.[1] He changed from a functioning human in one moment to a helpless, dumb invalid, "a case" in the next instant. Imagine an articulate author dependent for his livelihood on his use of language becoming totally unable to speak. Surely, the brain is wholly responsible for intelligence, capability, character, wit, humor, personality, and most of the characteristics that make us recognizable as individuals and as humans. Losing brain function can be dehumanizing and often makes individuals dependent on others. For these reasons, most individuals fear stroke more than any other disease, with the possible exception of cancer. Everyone would like to exit this life with their capabilities and mind intact, despite the inevitable aging of their bodies.

When I conjure in my own mind the personal tragedy of stroke, I picture one of my own patients, Dr Herman Blumgart, an extremely gifted physician, teacher, and investigator. He was, for many years, physician-in-chief at the Beth Israel Hospital in Boston.[11] His early investigations in coronary artery disease were landmark advances in the understanding of vascular disease of the heart.[12,13] He gave the annual introductory lecture to incoming Harvard Medical School students about the joys and responsibilities of being a physician. I recall his vivid, articulate lectures and bedside demonstrations. He was, in many ways, the model physician. He was also a vocal advocate on behalf of patients. His lecture "Caring for the Patient," presented in 1963 and reported in the *New England Journal of Medicine*, remains a model exposition on doctoring, as valid today as when it was originally delivered.[14] Tragically, this master of communication became in an instant, severely aphasic. His Wernicke-type aphasia was so severe that he could barely communicate verbally his basic needs and could hardly understand the queries and spoken and written statements of others. He could no longer read, eliminating one of his lifelong joys. As a junior staff neurologist, I was one of his physicians. The angst and frustration of his plight showed clearly on his face each time I saw him. This personal disaster was palpable and dramatic.

A brief history of stroke

In any human endeavor, the future is heavily influenced by the past. As the Wonderland dialogue between Alice and the Cheshire Cat (quoted at the beginning of this chapter)[2] teaches, if you want to get somewhere, you must know where you are going. If clinicians are to know where they are headed, they must know where they are, and where they and their predecessors have been. History adds an important dimension to knowledge. The past helps focus and broaden the perspective of the present and the future. Osler, and most other important medical innovators, were aware of their debt to history and of their inevitable entanglement with the past as well as the present and future.[3] I begin with a review of the history of stroke. Space necessitates inclusion of only a brief review of some important people and milestones to convey a sense of the historical context of the present state of knowledge about stroke. Of course, the following view of history is eclectic and personal and should be recognized as such.

Early observers: Hippocrates to Morgagni

Hippocrates (c. 400 BC) was probably the first to write about the medical aspects of stroke.[6,10] He and his followers were mostly interested in prognosis, predicting for the patient and family the outcome of an illness.[15–17] Hippocrates was a keen observer and urged careful observation and recording of phenomenology. Hippocrates wrote in his aphorisms on apoplexy, "persons are most subject to apoplexy between the ages of forty and sixty,"[16] and attacks of numbness might reflect "impending apoplexy."[10] He astutely noted, "when persons in good health are suddenly seized with pains in the head and straightaway are laid down speechless and breathe with stertor, they

die in seven days when fever comes on."[6,17] This description of subarachnoid hemorrhage shows the Hippocratic emphasis on observation and prognosis. Hippocrates also observed that there were many blood vessels connected to the brain, most of which were "thin," but two (the carotid arteries) were stout. The Greeks recognized that interruption of these blood vessels to the brain could cause loss of consciousness, and so they named the arteries *carotid*, from the Greek word Karos, meaning "deep sleep."

A few hundred years after Hippocrates, Galen (131–201 AD) described the anatomy of the brain and its blood vessels from dissections of animals. Although his early writings emphasized observation and experimentation, much of his later works combined mostly theorizing and speculation, in which he attributed disease to a disequilibrium between putative body humors and secretions such as water, blood, phlegm, bile, and so forth.[15] Galen and his voluminous writings dominated the 1300 years after his death. During the ensuing Dark and Middle Ages, persons who called themselves physicians gained their knowledge solely from studying the Galenic texts, considered at the time to be the epitome of all medical wisdom. Dissection, experimentation, and personal observations were discouraged and not considered scholarly.

Andreas Vesalius (1514–1564) challenged the Galenic tradition by dissecting humans and relying on his own personal observations instead of Galen's writings. Vesalius could not find the rete mirabile of blood vessels that Galen had described (presumably in a lower animal).[15] Vesalius's dissections were published in a volume entitled *De Humani Corpis Fabrica* (usually referred to as the *Fabrica*), which contained the detailed drawings his young artist and collaborator Jan Kalkar reproduced as woodcuts and copper plates.[6,18] The seventh book of the *Fabrica* contains 15 diagrams of the brain. These were the most detailed neuroanatomical studies up to that time.[6] By all accounts, Vesalius had a great flair for lecturing and teaching, and his works and personage stimulated much interest in anatomy and in the brain.[15]

During the last half of the seventeenth century, two important physicians, Johann Jakob Wepfer (1620–1695) and Thomas Willis (1621–1675), made further anatomical and clinical observations. Wepfer wrote a popular treatise on apoplexy that was originally published in 1658 and had five subsequent editions.[6,19] Wepfer performed meticulous examinations of the brains of patients dying of apoplexy. He described the appearance of the carotid siphon and the course of the middle cerebral artery in the sylvian fissure. Obstruction of the carotid and vertebral arteries was recognized as a cause of apoplexy (the blockage preventing sufficient blood from reaching the brain).[19,20] Wepfer was the first to show clearly that bleeding into the brain was an important cause of apoplexy. Thomas Willis (shown in Figure 1.2), a physician and neuroanatomist best known for his *Cerebri Anatome*, which contained a description of a circle of anastomotic vessels at the base of the brain, was also a well-known clinician and an astute observer. Willis was born soon after the deaths of William Shakespeare and Queen Elizabeth I when Great Britain was still basking in the artistic bloom of Elizabethan

Figure 1.2 Sir Thomas Willis (1621–1675).

England. Willis recognized transient ischemic attacks and the phenomenology of embolism, as well as the existence of occlusion of the carotid artery.[20–25] Willis described clearly the 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."[22] Willis was able to recruit a remarkable group of coworkers to Oxford, England, including the illustrator and architect Christopher Wren, and the physicists Robert Hooke and Robert Boyle.[24,25] These investigators were an important stimulus for science in post-Elizabethan England.[24]

During the eighteenth century, one of the true giants in medical history, Giovanni Battista Morgagni (1682–1771), was able to focus attention on pathology and the cause of disease. Up to that time, anatomy and prognostic formulas had prevailed. Morgagni, a distinguished professor of anatomy at the University of Padua, had a vision that the secret to understanding disease was to carefully perform necropsies on humans with illnesses and then to correlate the pathological findings with their symptoms during life.[15] Although the clinicopathological method is now taken for granted, this was a new approach for physicians in the eighteenth century. Morgagni labored his entire career to meticulously collect material for his epic work, *De Sedibus et Causis Morborum per Anatomen Indagatis*, which was published when he was 79 years old.[15,26] *De Sedibus* is a 5-volume work organized in the form of 70 letters to a young man describing the cases

collected. The first volume was titled *Disease of the Head*. Morgagni's clinical descriptions of patients were detailed but contained no formal physical or neurological examinations because these were not performed during his lifetime.

One of Morgagni's descriptions illustrates the style and content of the book:

> A certain man, who was a native of Genoa, blind of one eye, and liv'd by begging, being drunk, and quarreling with other drunken beggars, receiv'd two blows by their sticks; one on his hand which was slight, and another violent one at the left temple so that blood came out of the left ear. Yet soon after, the quarrel being made up, he sat down at the fire with them ... and again fill'd himself with a great quantity of wine, by way of pledge of friendship being renewed; and not long after, on the same night, he died.[15]

Necropsy showed a large epidural hematoma. Morgagni also described cases of intracerebral hemorrhage and recognized that paralysis was on the side of the body opposite to the brain lesion. Morgagni's work shifted the emphasis from anatomy alone to inquiry about diseases and their pathology, causes, and clinical manifestations during life.

The nineteenth and early twentieth centuries: Atlas makers, Virchow and Foix

During the early years of the nineteenth century, an influential treatise on apoplexy was written by a prominent Irish physician John Cheyne (1777–1836). Cheyne's book, which appeared in 1812, was titled *Cases of Apoplexy and Lethargy with Observations upon the Comatose Diseases*.[27] In it, he sought to separate the phenomenology of lethargy and coma from apoplexy. Cheyne's description of the neurological abnormalities was more detailed than those of his predecessors, and the "morbid appearances" of the patients' brains were emphasized after the example of Morgagni. One illustrative patient was a woman of 32 years who was near the end of her pregnancy. After a headache she became less responsive. Cheyne found that "she preserved the power of voluntary motion of the left side, but the right was completely paralytic. She seemed perfectly conscious, attempted to speak, but could not articulate; she signified by pointing with her left hand that she desired to drink."[27] After describing her case history, Cheyne discussed the available treatments (blood-letting, emetics, purges, and external applications) and then described 23 other cases. The pathological findings included clear descriptions of brain softenings and intracerebral and subarachnoid hemorrhages.[27] After Cheyne, developments were made concurrently in the clinical, anatomic, and pathological aspects of stroke.

John Abercrombie contributed a more detailed clinical classification of apoplexy in his general text published in 1828.[28] Abercrombie used the presence of headache, stupor, paralysis, and outcome to separate apoplectics into three clinical groups. In the first group, which he termed primary apoplexy, the onset was sudden, unilateral paralysis; rigidity and stupor were present, and the outcome was poor. These patients probably had large intracerebral hemorrhages or large brain infarcts. In the second group, patients had the sudden onset of headache, vomiting, and either faintness or falling but no paralysis. Undoubtedly, these patients had subarachnoid hemorrhages. In the third group, there was unilateral paralysis, often with abnormal speech, but neither stupor nor headache was present. This group must have had small infarcts or parenchymatous hemorrhages. Abercrombie also speculated on etiological mechanisms, mentioning spasm of vessels, interruption of the circulation, and rupture of diseased vessels causing hemorrhage.[10,28]

During the middle of the nineteenth century, dissemination of knowledge about the pathology of stroke came with the publication of four atlases, each containing plates of brain and vascular lesions. Hooper's atlas, published in 1828, clearly illustrated pontine and putaminal hemorrhages and a subdural hematoma.[29] Cruveilher (1835–1842),[30] Carswell (1838),[31] and Bright (1831)[32] also published atlases containing lithographs of systemic and neuropathological lesions. Bright, better known for his work on nephritis, collected more than 200 neuropathological cases and included illustrations of 25 nervous system specimens, including cerebrovascular cases, in his volume on nervous system disorders.[32]

During the latter half of the nineteenth century, the most important experimental and pathological information about vascular disease was published by Rudolf Virchow (1821–1902) (Figure 1.3), a pathologist working in Berlin.[15] He described the phenomenology 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 extremity veins in 18 patients and within the pulmonary arteries in 11, and reasoned that the bloodstream emanating from these veins must have been the conduit for transportation of the thrombi to distant sites such as the

Figure 1.3 Rudolf Ludwig Carl Virchow (1821–1902).

Figure 1.4 Charles Foix (1882–1927).

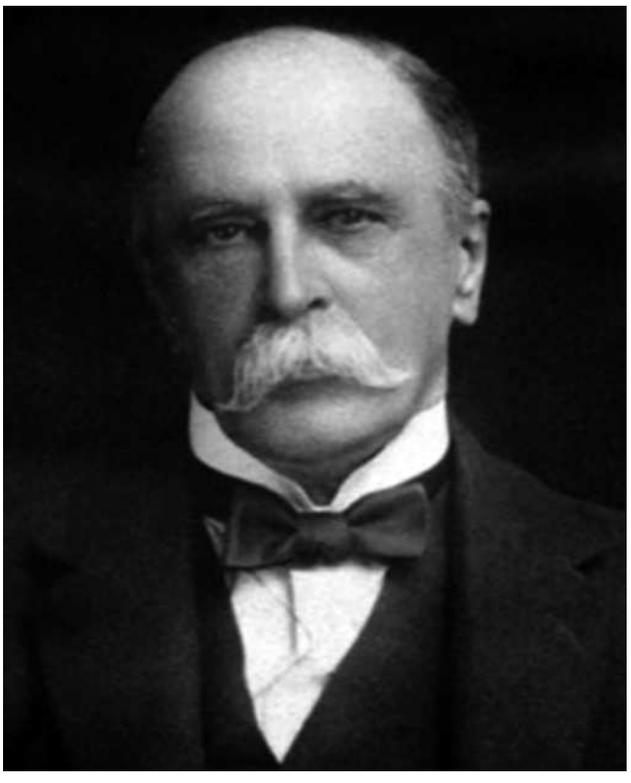

Figure 1.5 Sir William Osler (1849–1919).

arteries of the lung.[33,34] Virchow then used animal experiments to study the fate of foreign materials placed in veins. He later 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 showed systematically that in-situ thrombosis and embolism were the cause of infarction and that the process was unrelated to inflammation, the predominant theory at that time. Virchow described his classic triad of vascular thrombosis: (1) Stasis of blood in a vessel; (2) injury to the wall of the blood vessel; and (3) an abnormality in the balance between blood procoagulant and anticoagulant factors. Before Virchow's studies and reports, blood factors and thrombosis were given little attention.

During the later part of the nineteenth and the early years of the twentieth centuries, the anatomical details of the arteries supplying the brain were studied carefully. Detailed observations of the distribution of the arteries and veins in the cranium were made by Düret, a French neurosurgeon, first working in Charcot's laboratory;[35,36] by Stopford in Britain;[37] and later by Foix, who dissected pathological specimens at the Salpetrière in France.[38–41] Foix (Figure 1.4) made many key anatomical and clinical observations. Also during this same period, clinicians gathered more information on the clinical findings in patients with strokes that involved various brain regions. The bulk of these data involved clinical descriptions, with little interest concerning pathogenesis, laboratory confirmation, or treatment. The general medical and neurological texts of Osler,[42] Gowers,[43] and Wilson[44] contained detailed descriptions of the clinical findings and prognosis of many stroke syndromes. Sir William Osler (Figure 1.5), a famous internist, writer, and teacher, noted in detail the neurological findings in patients with bacterial endocarditis and described brain embolism in patients with rheumatic carditis. Osler first described the findings in patients with hemorrhagic telangiectasia (Osler, Weber, Rendu disease). The clinicopathological method culminated in descriptions by Foix and his colleagues of the syndromes of infarctions in the regions of the middle cerebral artery,[40,41] posterior cerebral artery,[41,45] anterior cerebral artery,[41,46] and vertebrobasilar arteries.[39,41]

Mid twentieth century and Miller Fisher

After Foix, a Canadian and American neurologist, C Miller Fisher (Figures 1.6–1.8), did much to awaken clinical interest in stroke. Fisher enlisted in the Canadian army during World War II and was captured and spent years in a prisoner-of-war camp. After the war, he was determined to make important contributions to medicine. His interest in stroke was tweaked by encounters with patients. One particular patient described in detail his episodes of transient monocular blindness that had heralded a hemisphere stroke. Fisher reviewed the literature and found scant reference to transient episodes before stroke. Fisher took meticulous thorough histories from patients hospitalized with stroke at a Veterans hospital in Canada and found that transient prodromal episodes were quite common. In patients with transient monocular blindness preceding stroke, Fisher reasoned that the causative occlusive process

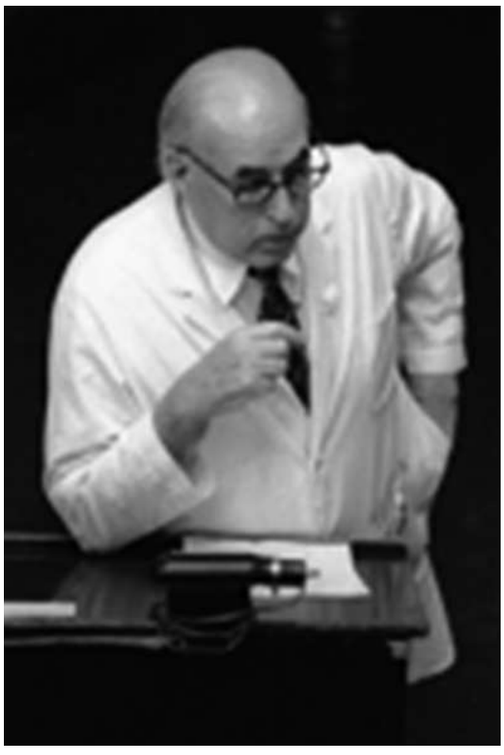

Figure 1.6 Charles Miller Fisher giving a presentation in 1978.

Figure 1.7 Charles Miller Fisher with Louis R Caplan in 1998.

Figure 1.8 Jay P Mohr, Charles Miller Fisher, and Robert Ackerman.

was likely in the internal carotid artery in the neck or head. A patient with transient monocular blindness then died suddenly. After death, Fisher dissected the neck and found, as predicted, that the internal carotid artery was occluded.[47] He then collected and reported series of patients with internal carotid artery occlusions and described in detail the clinical histories and neurological findings.[48,49] Fisher emphasized the frequent occurrence of warnings before stroke that he later dubbed transient ischemic attacks. "Prodromal fleeting attacks of paralysis, numbness, tingling, speechlessness, unilateral blindness, or dizziness often preceded and warned of impending strokes in patients with carotid artery disease."[9]

Fisher, like Foix, was both a pathologist and a clinician. During his early career in Canada, and later in Boston, he thoroughly examined at necropsy the neck and cranial arteries and their microscopic-sized branches. He obtained specimens of arteries from their origins from the aorta to their major intracranial branches. During the 1950–1990 period, Fisher made many major pathological and clinical observations on the pathological and clinical features of carotid artery disease;[48–52] the pathological and clinical aspects of intracerebral hemorrhage;[53–56] the pathological and clinical syndromes related to lacunar brain infarction;[57–59] and the clinical and pathological features of various posterior circulation neurological signs and brain and vascular lesions.[60–66] Before Fisher's major stroke publications, Raymond Adams, his mentor, had written a classic clinicopathological descriptive report with Charles Kubik on basilar artery occlusion.[67]

Fisher developed the first stroke fellowship in the United States and mentored many now senior stroke neurologists. I was fortunate to serve as his stroke fellow during 1969–1970. Figure 1.7 is a recent picture of Miller Fisher and I. Dr Jay P Mohr, who worked with me in developing and maintaining the Harvard Stroke Registry in the early 1970s, and a leader in the field of stroke trials, was another of Dr Fisher's stroke fellows. Dr Robert Ackerman, a pioneer in the early field of PET scanning and stroke, and in the non-invasive evaluation of stroke risk was a trainee and later colleague of Dr Fisher and was the organizer of the Boston Stroke Society for three decades. Mohr, Fisher, and Ackerman are shown in Figure 1.8. Ackerman also trained stroke fellows including several future leaders in the field: Geoffrey Donnan and Steven Davis (Australia); Jean-Claude Baron (France and UK), and James Grotta and Viken Babikian (United States).

Fisher's reports contained meticulous descriptions of the signs and symptoms found in patients with infarcts and

hemorrhages in various vascular and brain distributions. Elegant and thorough as these descriptions were, their limitations included: (1) Reliance on only the fatal cases because precise diagnosis was not possible during life; (2) predominance of anecdotal cases, with few data on the incidence and frequency of findings in large series of patients with the specific described conditions; (3) insufficient availability of technology to allow accurate diagnosis or clarification of the pathogenesis or pathophysiology of the vascular lesions and their effects on the brain; and (4) little information about the effectiveness of various treatments.

1975 to present

During the last quarter of the twentieth century, there was an explosive growth of interest in and knowledge about stroke. Advances in technology allowed better visualization of the anatomy and functional aspects of the brain and of vascular lesions during life. Databases and registries of large numbers of well-studied stroke patients helped identify and quantify the most common clinical and laboratory findings in patients with various stroke syndromes. Epidemiological studies identified more accurately the risk factors for stroke and suggested prevention strategies. New surgical and medical treatments were now possible. 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 arterial lesions including atherosclerotic stenoses, aneurysms and vascular malformations. Other devices could be used to retrieve thromboemboli that blocked arteries in the neck and head. 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

The technological revolution probably began with the work of the Portuguese neurosurgeon Egas Moniz (1874–1955). Moniz surgically exposed and temporarily ligated the internal carotid artery in the neck and then rapidly injected by hand a 30% solution of sodium iodide, taking skull films later at regular time intervals.[68] He first used the technique for studying patients suspected of having brain tumors, but he later studied stroke patients. By the time of his monograph on angiography in 1931,[69] Moniz had studied 180 patients; had switched to another opaque-contrast agent, Thorotrast, because of convulsions that had occurred after the injection of sodium iodide; and had demonstrated the occurrence of occlusion of the internal carotid artery during life.[68,69] Modern angiography began with the work of Seldinger in Sweden, who devised a technique by which a small catheter could be inserted into an artery over a flexible guidewire after withdrawing the needle.[70,71] Catheter angiography of selected vessels in the carotid and vertebral circulations was then possible without surgical incisions. Newer dyes and filming techniques have since made angiography safer and more definitive.

Hounsfield of the research laboratories of Electrical 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.[6] CT scanners were first introduced to North America in 1973. Films from first-generation scanners were quite primitive, but by the late 1970s, third-generation scanners had made CT a useful, almost indispensable, diagnostic technique. By the mid 1980s, CT was readily available throughout North America and most of Europe. CT allowed clear distinction between brain ischemia and hemorrhage and allowed definition of the size and location of most brain infarcts and hemorrhages. The advent of magnetic resonance imaging (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[72] and CT angiography.[73]

Ultrasound was introduced into medicine in 1961 by Franklin and colleagues, who used Doppler shifts of ultrasound to study blood flow in canine blood vessels.[6,74] B-mode ultrasound was soon used to provide images of the extracranial carotid arteries non-invasively. By the early 1980s, B-mode, continuous-wave (CW), 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).[75] TCD made possible non-invasive detection of severe occlusive disease in the major intracranial arteries during life, as well as sequential study of these lesions.[76]

Introduction of echocardiography and ambulatory cardiac rhythm monitoring in the 1970s and 1980s greatly improved cardiac diagnoses and detection of cardiogenic 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. Accurate diagnosis using modern technology facilitated clinical-imaging correlations in patients with non-fatal strokes, and this paved the way for monitoring the effects of various treatments. By the end of the twentieth century, advanced brain imaging with CT, MRI, and newer magnetic resonance (MR) modalities,

including fluid-attenuated 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. During the first decades of the twenty-first century, high-resolution MR and CT studies of lesions imaged in cross-section could better define the nature of atherosclerotic plaques and other arterial wall abnormalities. Cardiac and aortic sources of stroke were studied using transesophageal echocardiography. More sophisticated 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.

Data banks and stroke registries

During the middle years of the twentieth century, clinicians had advanced knowledge of clinical phenomenology by personally studying and describing small groups of patients. In 1935, Aring and Meritt studied a group of patients coming to necropsy at the Boston City Hospital to clarify the differential diagnosis between brain hemorrhages and infarcts.[77] Fisher and his colleagues and students studied and described the clinical findings in small numbers of patients with various cerebrovascular syndromes. During the 1970s and 1980s, the technological advances described made it possible to define the clinical and laboratory features of non-fatal, even minor, strokes and pre-stroke vascular lesions. With better knowledge of clinical and morphological 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 of stroke patients began with the series of Dalsgaard-Nielsen in Scandinavia[78] and with series of patients seen by clinicians at the Mayo Clinic in Rochester, Minnesota.[79,80] The Harvard Cooperative Stroke Registry in the early 1970s was the first computer-based registry of prospectively studied stroke patients.[81] Other stroke registries and databases were developed around the world and provided more quantitative information about clinical and laboratory phenomena and diagnoses.[82–89] Community-based studies in south Alabama[90]; Framingham, Massachusetts[91]; Oxfordshire in Great Britain[92]; the Lehigh Valley in Pennsylvania[93]; and various regions in North Carolina, Oregon, and New York[94] generated important epidemiological data. Computer-based registries and data banks have undoubtedly assisted collection and analysis of a wide variety of clinical, radiological, pathological, and epidemiological information.[95,96] Especially important has been recognition of various risk factors that predispose to stroke. The present text relies heavily on data from these studies, especially those in which I was personally involved.[81,83,85]

Stroke units, stroke specialists, and stroke nurses

During the nineteenth and the first two-thirds of the twentieth century nearly all acute stroke patients were cared for in the general wards and rooms of hospitals. There were very few stroke specialists and no stroke nurse specialists. Some rehabilitation units, almost entirely outside of acute hospitals did specialize in stroke rehabilitation. During the 1960s and 1970s Neurology departments began to be split off from Departments of Internal Medicine within academic medical centers in the United States and Europe. When this occurred, hospitals with neurology departments began to place stroke patients and other patients with neurological diseases on neurology wards and private rooms while other stroke patients continued to be treated on medical services scattered throughout the hospitals. During the 1970s and 1980s, hospitals placed very sick patients requiring frequent monitoring and care into specialized intensive care units (ICUs). Cardiac, surgical, and medical ICUs were first formed. Neurosurgeons and neurologists in large medical centers were successful in creating Neuroscience ICUs manned with nurses specially trained to care for very ill and acute neurological disorders including stroke. A new neurological specialty – neurology intensivists began to grow.

A number of factors during the 1980s and 1990s conspired to promote the development and proliferation of specialized stroke units. CT, MRI, ultrasound, and vascular imaging capabilities made it clear that strokes were complex and composed of very diverse etiologies and pathophysiologies. Moreover specific diagnosis could be made rather quickly and safely but required special training, expertise, and experience. Funding for trials made it possible in academic medical centers to hire nursing coordinators. The development of managed care strategies in hospitals in the United States forced more rapid and efficient care and throughput of stroke patients. Newer therapies, surgeries, percutaneous interventions, and especially thrombolysis made it advantageous to segregate stroke patients in ICUs and specialized stroke units.

These specialized units were composed of nurses with experience and training in stroke, internists, and stroke neurologists. These stroke units were able to deliver: specialized nursing care; attention to management of blood pressure, fluid volumes, and other physiological and biochemical factors; protocols and practices to facilitate rapid and thorough evaluation and treatment, monitor treatment, carry out randomized therapeutic trials, and prevent complications; education about stroke and its prevention to patients and their families and caregivers.[97–100] They also promoted an up-beat optimistic view of stroke recovery in contrast to the situation previously present on medical wards where stroke patients were often considered undesirable patients with hopeless outcomes.

Once these units began to proliferate especially in Europe, it became clear that they were an important major advance.

Dedicated stroke units have been convincingly shown to decrease mortality, limit stroke morbidity, and allow more patients to retain their independence and to return home after stroke.[101–103] Between the carrying out of the two large European thrombolytic trials (ECASS I and ECASS II),[104,105] neurologists in the hospitals engaging in these trials developed dedicated stroke units. These units attended to the general medical care of the stroke patients and prevention of complications. As a result the morbidity in both the thrombolytic treatment group and the placebo groups improved dramatically in the ECASS II trial and the good results in the placebo-treated group exceeded that of any prior thrombolytic trial. The milieu and the care in dedicated stroke units leads to better outcomes. Mortality is reduced. More patients return home and less are transferred to chronic hospitals and nursing homes. Short-term and long-term functional outcomes are also improved. There is no longer any doubt that stroke units work. One of the the most important therapeutic advances during the last decades of the twentieth century in the treatment of patients with acute stroke was the development of stroke services, stroke nurses, stroke specialists, and stroke units.

Advances in medical and surgical therapy and randomized trials

During the first half of the twentieth century, researchers discovered the anticoagulant effects of warfarin and heparin compounds. McLean, a medical student at Johns Hopkins, first isolated an anticoagulant compound from body tissues.[6,106] Howell and Holt extended Mclean's research and named the new compound heparin.[6,107] Link and colleagues found that a natural coumarin compound found in hay was transformed during spoilage into a substance that led to bleeding in cattle.[6,108] Link crystallized dicumarol in 1939, and soon thereafter many laboratories synthesized related warfarin-type compounds that could be used therapeutically.[6] During the 1950s clinicians began to give these anticoagulants to patients with various clinical syndromes mostly based on the tempo of brain ischemia – transient ischemic attacks, progressing stroke, completed stroke, etc.

One of the first randomized therapeutic trials concerned the effectiveness of anticoagulant therapy in patients with various ischemic syndromes.[109] This trial, which was reported in 1962, contained only 443 patients, 219 of whom were anticoagulated.[109] The methodology and analysis used in this trial would be considered rather primitive by today's standards. Treatment was open label, not blinded, the number of patients in each ischemic group was very few, and the endpoints varied depending on the nature of the group; for example, in patients entered in the group "thrombosis-in-evolution" (128 patients) the investigators analyzed progression of infarction and mortality. This study antedated CT scanning so that estimates of progression of infarction were only clinical. During the last decades of the twentieth century many trials studied the utility of anticoagulation in a variety of causes of brain ischemia, especially prevention of stroke in patients with atrial fibrillation.[110–113]

Sparked by clinical observations, clinicians in the mid twentieth century turned to drugs that affect platelet functions as an alternative to heparin and coumadin. Probably the first clinical observations on the potential anticoagulant functions of aspirin were made by Craven who noted that dental patients bled more if they had used aspirin.[6] He urged friends and patients to take 1 or 2 aspirin tablets a day and later published the effectiveness of this strategy in preventing coronary and cerebral thrombosis among 8000 men in articles during the mid 1950s in the *Mississippi Valley Medical Journal*.[114,115] Case reports from the United States and Britain on the effectiveness of aspirin in preventing attacks of transient monocular blindness brought the subject to more general attention.[116,117] The American[118] and Canadian[119] aspirin trials soon followed during the 1970s. These studies were the first of many trials of various antiplatelet agents almost invariably studied in large numbers of patients lumped together as having transient ischemic attacks or minor strokes.

Subsequent trials studied the relative safety and efficacy of aspirin versus warfarin in preventing stroke recurrence in a large numbers of ischemic stroke patients, the WARSS (Warfarin–Aspirin Recurrent Stroke Study) trial,[120] and in patients who had brain ischemia attributable to severe intracranial arterial stenosis, the WASID (Warfarin–Asprin Symptomatic Intracranial Disease) trial.[121] Physicians became increasingly aware that warfarin compounds were difficult to use in practice. These vitamin K inhibitors worked indirectly on the coagulation system, were affected by other medications and foods, and were difficult to keep in target range of optimal anticoagulation. As a result many patients were intermittently under anticoagulated and at risk for brain ischemia, and bleeding was an important problem. Multiple frequent blood tests were needed to monitor anticoagulation. Because it took time for warfarin to become clinically effective, heparin was customarily used until patients were effectively anticoagulated with warfarin. Pharmaceutical companies placed on the market newer anticoagulants that were direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (apixaban, rivaroxaban, edoxaban). These agents were all taken orally, worked quickly so that heparin was not needed initially, had fixed doses so that long-term blood test monitoring was not essential, and were not as affected by other agents and foods as the vitamin K inhibitors. Trials of these agents tested their safety and efficacy versus warfarin in patients with atrial fibrillation, a known important cause of brain embolism.[122–125] These newer anticoagulants caused less intracranial bleeding and were at least as effective as warfarin in stroke prevention.

Miller Fisher in his seminal reports on carotid artery disease in the early 1950s predicted that one day in the future surgery would be feasible on the internal carotid artery to prevent stroke.[47,49] During the 1950s, surgeons reported their experience with surgery on the internal carotid[126–128] and other extracranial arteries.[6,129–131] In order to study the effectiveness of surgery on the extracranial arteries, a host of neurologists and adventurous surgeons led by Dr William S Fields organized and carried out a large surgical trial during the 1960s.[132,133] The trial was entitled the Joint Study of

Figure 1.9 William S Fields (1913–2004).

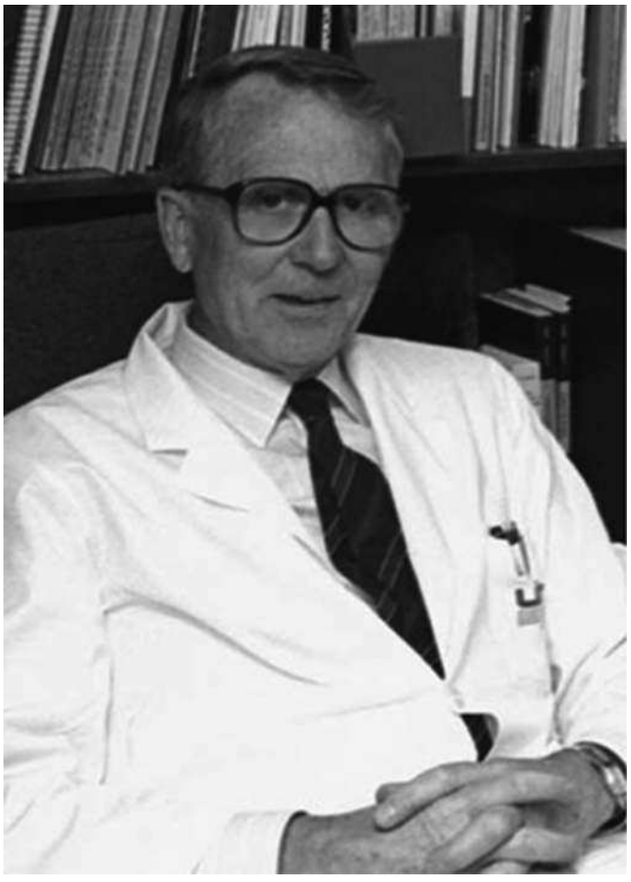

Figure 1.10 Sir Henry J M Barnett. From Barnett HJM (ed), *Cerebrovascular Disease*, Neurological Clinics Vol 1, No. 1. Philadelphia: W B Saunders, 1983.

Extracranial Arterial Occlusions and was supported by the National Heart Institute. This was the first surgical versus medical treatment trial carried out in the United States in which 6535 patients were randomly assigned to surgical versus non-surgical treatment. Mortality in this trial was equal in the medical and surgical groups and death was most often cardiac. Fields (Figure 1.9) was a pioneer in the study of cerebrovascular diseases, hosted and published many conferences in Houston about various stroke conditions, and was the principal investigator and organizer of pioneering stroke trials.[6,134,135]

During the 1960s and early 1970s Donaghy and his colleagues devised a microsurgical technique to anastamose small arteries together.[136,137] One of their trainees, Gazi Yasargil, was mostly responsible for bringing this technique into clinical practice when he created surgical extracranial-to-intracranial (EC-IC) shunts to treat patients with occlusive vascular disease who had brain ischemia.[138–140] By 1977 bypass procedures usually anastamosing the superficial temporal artery to branches of the middle cerebral artery were being performed widely in the United States and Europe. Henry Barnett (Figure 1.10) organized and performed a trial of these EC-IC bypass procedures, and showed that the procedure as performed at the time was less successful than medical treatment.[141] The results of this trial, published in 1985, drastically reduced the number of these procedures performed. Because neurologists and surgeons continued to posit that some patients with symptomatic atherosclerotic internal carotid artery occlusion and hemodynamic cerebral ischemia were at high risk for subsequent stroke when treated medically, a trial was carried out testing the efficacy of bypass in patients with cerebral ischemia identified by ipsilateral increased oxygen extraction fraction as measured by positron emission tomography (PET).[141,142] The trial was terminated early for futility because of the high rate of ipsilateral ischemic strokes within 30 days of creation of the surgical bypass.[141,142]

Alarmed that the number of carotid endarterectomy cases was growing out-of hand, Henry Barnett organized a trial of surgical versus medical treatment for patients with symptomatic carotid artery disease. This North American Symptomatic Carotid Endarterectomy Trial (NASCET)[143,144] and the concurrent European Carotid Surgery Trial (ECST)[145,146] showed the effectiveness of carotid endarterectomy in selected patients with selected lesions performed by surgeons who had low surgical mortality and morbidity results. Trials of carotid surgery in patients who had no related symptoms soon followed in both the United States[147] and Europe.[148,149] Carotid surgery and stenting were later compared in the CREST (Carotid Revascularization Endarterectomy Versus Stenting) Trial in the USA.[150,151]

During the last decades of the twentieth century there was an almost religious zeal for randomized clinical trials. Some enthusiasts saw the future dominated by doctors searching computer databases of trials to choose what to do