A Career in Cerebrovascular Disease
A Personal Account
C. Miller Fisher, MD

The Editor, when inviting this piece, thought that an account of my entry into the stroke field and the unfolding of the subsequent studies in cerebrovascular disease would be instructive for the younger readers of Stroke. Be that as it may, knowledge of how a specialty has evolved can be useful in placing present endeavor in perspective. The story is one of clinical and neuropathological studies carried out by one person, an approach now largely superseded.

Boston City Hospital

In 1949, after my completing a fellowship in Neurology at the Montreal Neurological Institute, Dr Wilder Penfield recommended a year of postgraduate work abroad. Dr Roy Swank, a colleague, insisted that a period of study on the Neurology Service of the Boston City Hospital (BCH) under the direction of Dr Derek Denny-Brown and Dr Raymond D Adams would be unparalleled. Dr Swank placed a telephone call and in a minute or two it was arranged that I spend a year in Neuropathology at BCH under the guidance of Dr Adams. The subject to be investigated was acute hypertensive encephalopathy. A grant-in-aid was received from the Multiple Sclerosis Society. It was for $100.

In 1949 BCH was one of the world’s premier medical centers: 2000 beds and 3 academic medical services, Harvard Medical School, Boston University, and Tufts Medical School. Enthusiasm was the order of the day. The Department of Pathology, including the Section of Neuropathology, comprised the Mallory Institute of Pathology. It was a busy service, with 900 autopsies performed each year. In addition, the Coroner’s Office was housed in the Institute. In Neuropathology 700 to 800 brains were examined yearly. The abundance of pathological material would be an important factor.

Two residents in Neuropathology were responsible for the day-to-day work: Dr David McDougall, the senior, and myself. Dr McDougall developed formalin dermatitis on his hands and was forbidden from placing brains in formalin for fixation and from sectioning the formalin-fixed brains. It therefore devolved on me to section all brains, with Dr McDougall standing behind, directing the proceedings. Experience accrued rapidly, as we examined 2 or 3 brains daily. One afternoon about 2 months after my arrival in the Department of Neuropathology, 9 brains had accumulated for examination that day. We were scheduled to start at 1 PM, but Dr McDougall had not arrived. While waiting, to pass the time, I inspected the middle cerebral arteries (MCAs) at the base of the brain as they ran laterally in the Sylvian fissure. The arteries were patent. (The routine method of examining the brain was to cut it into a series of coronal sections about 1 cm thick. If study of the arteries was later indicated, the vessels were traced out, but with some difficulty, since their continuity was interrupted as they passed from one coronal section to the next.) Dr McDougall arrived, and the first brain was routinely sectioned coronally. The sections showed a large hemorrhagic infarct in the territory of the right MCA. Examination of the vessels that had been cut across as the brain was sectioned showed no blockage. An explanation for the infarct was not obvious. Brain 3 that afternoon, when sectioned, also showed a large hemorrhagic infarct in one MCA territory. I casually guessed, from having dissected out the arteries in continuity in brain 1, that we would not find an arterial obstruction in brain 3. Dr McDougall demurred, but a careful search through the sectioned arteries revealed no obstruction. As it turned out that afternoon, brain 9 showed the same picture as brains 1 and 3, a hemorrhagic infarct and no blockage of the arteries supplying the territory of the infarct. The general pathological examination in all 3 cases showed hemorrhagic infarcts in the kidneys and spleen. The clinical records indicated that in all 3 cases, the patient had been in atrial fibrillation (AF). In attempting to fit the pieces of the puzzle together, it was tentatively suggested that emboli had arisen in the heart and were carried to the arteries of the brain, kidneys, and spleen, where they gave rise to infarcts. The emboli then disappeared from the arteries by the time the patient died. Second, it was suggested that hemorrhagic infarction might be a sign of cerebral embolism. It turned out that these suppositions were correct, although a vast literature had to be reviewed in the meantime.1 Two pathological findings that had been puzzles for a century were explained in one afternoon. It was all a matter of an abundance of pathological material and the examination of 9 brains at one sitting.

The doctrine of dissolution of emboli in cases of AF was found to apply in brain, kidney, spleen, mesenteric arteries, and the peripheral arteries. Pulmonary emboli could also undergo lysis or migrate distally after causing an infarct, an occurrence that led Virchow to question whether pulmonary infarcts were always the result of embolism from the peripheral veins.

The study of cerebrovascular disease and strokes has a long history. Cerebral infarcts and hemorrhages served as the basis for the elucidation and localization of many cerebral functions: motor function, sensation, aphasia, apraxia, blindness,
hemianopia, anosognosia, the brain stem syndromes, the lateral medullary syndrome etc. The clinical syndromes associated with each cerebral artery were accurately described. Kubik and Adams\(^2\) published their classic description of basilar artery occlusion in 1946. What had not been investigated in the past was the pathology of the cerebral vessels and the mechanism of the infarction. Because there was no special therapy for strokes, there was little interest apart from the neurological signs. The treatment of high blood pressure was lumbar sympathetic or a rice diet. Penicillin had just become available for use when pneumonia complicated a stroke. A 6-month survey of stroke patients coming to autopsy at BCH showed that the clinical interpretation of the nature of the stroke, usually thrombosis of an MCA, was incorrect in all cases. In 1950 an authoritative study\(^3\) concluded that approximately 70% of ischemic strokes were due to vasospasm, ie, the artery leading to the infarct was patent and no cause was apparent. If the doctrine of dissolution of emboli in cases of AF was correct, a large proportion of strokes ascribed to vasospasm would find an alternative explanation. It soon was apparent that thrombi associated with cerebral atherosclerosis did not undergo lysis, and it became possible in many cases to distinguish thrombosis from embolism pathologically.

**The Montreal General Hospital**

On my return to Montreal at the end of 1949, Dr Francis McNaughton, Chief of Neurology at the Montreal General Hospital arranged for me to continue the neuropathological study of strokes in the Department of Pathology at that hospital. The Director of Pathology, Dr Joseph Pritchard, could not have been more helpful. It was also arranged that I attend on the Neurology Service of the Montreal Veterans Hospital. Shortly after returning to Montreal, I examined at the neurology clinic of the Veterans Hospital a veteran who had suffered a rather severe left hemiplegia 2½ years before. He related that in the weeks before his stroke, he had several times become temporarily blind in one eye. While I was writing my note he said “Isn’t it funny, I went blind in the wrong eye? I am paralyzed on the left side, and I went blind in the right eye.” That fragment of history had no special meaning and was probably interpreted as a hemianopic phenomenon inaccurately recalled by the patient. But a week later another hemiplegic veteran gave an almost identical story. He said that before his stroke he was in his favorite tavern and told his friends that he had just gone blind in one eye. They reassured him that everybody has those things. “Don’t worry, it will be alright in a minute.” And it was. It, too, was on the “wrong” side. Stroke patients were then routinely asked about this event, and soon another patient gave a similar story. In casting about for an explanation, it was evident that the stroke and the monocular blindness occurred in strokes involving each of the cerebral arteries, MCA, anterior cerebral artery (ACA), posterior cerebral artery (PCA), and basilar artery (BA). From this there arose the possibility that prodromal symptoms could provide the opportunity to intervene before the full stroke occurred. Tentative anticoagulant trials starting at the stage of premonitory symptoms were begun. Interestingly, the brief spells associated with strokes had in the past also been attributed to vasospasm.

A patient with basilar artery thrombosis with a stuttering course and numerous transient symptoms was treated with intermittent heparin and coumadin. While receiving anticoagulants, all transient phenomena ceased and the patient was much improved. On stopping anticoagulants, the transient spells soon resumed, ceasing again when anticoagulants were reinstituted. The spells were presumably ischemic in nature rather than vasospastic, and the term transient ischemic attack (TIA) was suggested.\(^4\)\(^5\) At this patient’s death 6 years later, pathological study showed total occlusion of the midportion of the BA. When it seemed that a treatment for strokes was available, accurate diagnosis became essential.

The routine removal of the carotid arteries from the neck at autopsy was begun, and after removal of 100 pairs it became clear that disease of the ICA in the neck accounted for a significant number of strokes. Another fraction of the “vasospasm category” could be accounted for. One day at luncheon Dr R.R. Fitzgerald, who had just returned from a national surgical meeting in New Orleans, described the remarkable surgical procedures being performed on the iliac arteries. This prompted the suggestion that the carotid plaque because of its
strictly focal extent should be amenable to a surgical bypass procedure.

Post mortem removal of the carotid arteries from the neck continued until 1100 pairs had been removed.6,7 Often, the removal extended to and included the arch of the aorta, and not infrequently the vertebral arteries also were resected. This was the first sortie into the clinicopathological correlation of vascular disease of the arteries of the neck.

In one of the first carotid occlusion cases, the brain showed a striking watershed, or borderzone infarction, extending from near the frontal pole back to the parietal lobe. The mechanism of this type of infarct had heretofore been obscure. Recognition of this principle became important in understanding cerebral blood flow patterns and interpreting the localization of cerebral infarction and TIAs.

In embolic strokes associated with AF, most often no thrombus was found in the left atrium that might have been the source of the embolus. In attempting to explain this paradox, serial sections of the left atrial appendage were prepared in a series of cases. In every case mural thrombus, not obvious to the naked eye, was found in the interstices of the trabeculae carnaeae.8

As neuropathologist to a large chronic-care facility, I was provided the opportunity to study postmortem the brains of many demented patients and compare the findings with those from nondemented patients of the same age bracket. It was possible to demonstrate unequivocally that cerebral artery disease played no part in the pathogenesis of slowly progressive chronic dementia, which at that time was commonly attributed to “hardening of the arteries.” Furthermore, cerebral arterial disease played no role in Alzheimer’s disease.5,9

During this period (1950 to 1954), the superabundance of lacunar lesions in the brains of arteriopathics became evident.10 The importance of high blood pressure as their cause was clearly demonstrated. Lacunes had been a well-known pathological entity since the mid-1800s, but their nature remained unclear. Ischemia was favored by Marie, but the causative lesion had not been identified. Tracking down the pathogenesis would take some 15 years. It was mainly a technical problem of devising a practical system of studying the small cerebral arteries that supplied the territory of the lacune. There was no CT or MRI. Investigation could begin only when a lacune was found on postmortem brain sectioning, but by that time the prosecutor’s knife had disturbed the fine anatomy and probably severed the arteries to be studied.

Allusion has been made to the traditional routine of sectioning the brain in coronal slices when studying it pathologically. This severs the major cerebral arteries into multiple small segments, almost precluding a thorough examination. By the time the lesions within the brain are revealed, the arteries have already been sectioned. Furthermore, in cerebral sectioning the brain is cut in the plane of the deep penetrating arteries that run to lacunes, which makes tracing out the course of the arteries literally impossible.

The vascular examination of the brain postmortem was greatly facilitated when the method of horizontal sectioning was introduced. A single cut entering just above the frontal poles and exiting 1 cm above the occipital poles samples a large part of the deep regions of the brain while leaving long reaches of the major cerebral arteries intact for examination. A horizontal section will reveal the pathological lesions, while the arteries can still be examined in detail. Important for present purposes, a horizontal section often reveals 1 or more lacunes, leaving the penetrating arteries intact or with 1 severance as they run in a vertical plane to reach the basal ganglia and thalamus. There was the possibility that arteries to lacunes could be traced in continuity.

In the 1950s most neuropathology laboratories in preparing microscopic sections used the celloidin embedding technique. Usually there was an interval of 3 months between the gross examination of tissues and the availability of microscopic sections. In studying the vascular disease that caused lacunar infarcts, it became clear that serial sections would be necessary. The celloidin technique would prove too time consuming, too inaccurate, and too complicated. A change to paraffin embedding was necessary. Through trials using one method of serial sectioning after another, it was concluded that to study lacunar infarcts adequately it would be necessary to prepare continuous, uninterrupted serial sections of large blocks of cerebral tissue, anticipating that a lacune lay within. All sections would have to be stained and, most importantly, only 1 stain could be used lest the order of the slides be lost. Developing a reliable routine consumed some 15 years. Each lacune entailed the preparation of several thousand sections. The early trials were begun in Montreal, and the project was continued in Boston on my return there in 1954.

Massachusetts General Hospital
At the Massachusetts General Hospital (MGH), a stroke service of sorts was formed in 1954. Two or 3 stroke fellows and I consulted on stroke cases throughout the hospital. Usually, the cerebrovascular patients in the hospital outnumbered the patients on the rest of the neurology and neurosurgical services combined. Initially, the reliability of an accurate clinical diagnosis supported by skull x-ray and lumbar puncture must have approached zero. Our attention was first drawn to intracranial hemorrhage, with the prospect that neurological intervention might be feasible. However, we were unable to localize the site of the hemorrhage accurately enough to guide the surgeon. Over a period of 3 years, the clinical signs of thalamic, pontine, and cerebellar hemorrhages11,12 were established with fair reliability. The picture of cerebellar hemorrhage became clear enough to allow the surgeon to operate as an emergency without laboratory investigation.13 Dr Peirson Richardson, the MGH neuropathologist, permitted the stroke service to conduct the pathological studies in stroke cases.

A stumbling block in assessing our sickest stroke patients was the lack of a neurological method of examining the stuporous-comatose patient. At the time, such patients were usually nursed in the swimmer’s semiprone position, and the only neurological examination consisted of noting the general reaction to pinching. From 1954 to 1960, the comatose patient was subject to a methodical study in which assessment of all reflex responses was used to analyze the state and determine a coma scale. For the first time it became feasible to measure and monitor to any extent changes in this rather vast clinical, heretofore unmapped neurological territory.14

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In this same period, the clinical syndromes associated with occlusion of each of the major cerebral arteries were delineated. Data were collected on the clinical characteristics of TIAs associated with strokes in each of the cerebral artery territories. A classification of TIAs was drawn up. The numerous phenomena that had to be differentiated from TIAs required the same careful study. The mechanism of TIAs, embolism versus failure of flow, became a matter of debate that continues to the present time. It was the conclusion of the stroke service that multiple TIAs of the same pattern are associated with arterial stenosis and are flow related, not embolic. Many objections were raised against the embolic theory. Thromboangiitis obliterans was a common diagnosis in circulatory disturbances of the legs, and to a lesser extent of the brain. From the vantage position of the autopsy room, it was shown that that diagnosis in most instances was incorrect. In the case of the brain, the arterial process proved to be the result of unrecognized disease of the ICA. An extensive clinicopathological study of the lateral medullary syndrome was completed. A report in the literature that Creutzfeldt-Jakob disease was a form of vascular disease prompted an investigation into that illness. No evidence supporting the vascular claim could be adduced.

The exploration of anticoagulant therapy begun in Montreal was continued with diagnostic inaccuracy being the main hazard. Thrombotic strokes at the stage of TIAs, or during the period of evolution, were treated with bolus heparin intravenously at 4-hour intervals, followed by long-term coumadin. We were impressed with the benefits. In 1957 a National Cooperative Study of anticoagulant therapy was organized to determine its value in all types of ischemic cerebrovascular disease. It was the first scientifically randomized therapeutic trial in neurology. Again, inaccuracy of diagnosis was the main obstacle. In only a few cases was angiography used. The study, which involved 7 centers, was discontinued after 3 1/2 years of randomization because of the number of fatal hemorrhages related to anticoagulation. Much valuable experience with strokes was gained. It is my impression that the use of intravenous bolus heparin therapy has still not been thoroughly tested.

Lacunar Strokes

Gradually, the clinicopathological correlations of the various lacunar strokes emerged. To achieve a correlation, first the patient had to be examined in the acute stage of the stroke. Lacunes were consistent with long survival, and death, when it came, had to occur with the patient still under our care. Permission for an autopsy had to be obtained. Not infrequently, further lacunes had occurred, which confused the correlation, or a hypertensive hemorrhage had destroyed the region of the lacune. Finally, the brain had to be reserved for special pathological examination by the stroke service. Pure motor hemiparesis or hemiplegia associated with an infarct involving the posterior limb of the internal capsule was among the first syndromes to be identified. During this sorting-out process, an interesting phenomenon was seen. Clinicians were so accustomed to diagnosing a sensorimotor hemiparesis that even several years after recognition of pure motor hemiparesis, experienced neurologists would find sensory impairment in a case of pure motor hemiparesis when none existed. We are liable to find what we expect rather than what exists. Thus, identifying cases of pure hemiparesis was not a simple matter. Pure sensory stroke involving the face, arm, and leg was linked to a thalamic lacunar infarct. The cause of ataxic hemiparesis was traced to a lacunar infarct in the basis pontis at the junction of the upper one third and the lower two thirds. One of the first lacunar strokes for which the lacune was found was the dysarthria–clumsy hand syndrome. The localization in the pons was a complete surprise. With the discovery of CT imaging in 1973 and MR imaging in 1982, as much progress could be made in 1 year as in 20 years before their introduction. A pathological study showed that the incidence of lacunes at postmortem decreased greatly compared with a study 25 years before, probably reflecting improved treatment of high blood pressure. The condition \textit{état lacunaire} became a rarity, and in retrospect it is doubtful that it was ever a valid clinicopathological entity.

By using the serial sectioning technique described previously, the first satisfactory study of the entire vasculature of a lacunar infarct was achieved in 1965. Lacunes were clearly small infarcts. The small distal arteries remaining within a lacune could be traced in continuity (the sections were 8 \(\mu\)m thick) to confluence with larger and larger branches until the entire volume of the infarct was accounted for. The main feeding artery could then be followed proximally until the site of the occlusion was found. In the first successfully studied case, it was a small atheroma in an artery 500 \(\mu\)m in diameter. The remaining narrowed lumen was occluded by a tiny thrombus attached to the atheroma. The occluded artery was a small penetrating branch arising from the stem of the MCA. In the following 15 years, approximately 25 symptomatic lacunar infarcts were studied in the same manner. Four types of penetrating artery occlusion were found: (1) occlusion by an atheroma with superimposed thrombus as just described; (2) blockage of the mouth of a penetrating artery by atheroma in the wall of the parent artery; (3) dissection in the wall of the parent artery, causing obstruction of the penetrating vessel; and (4) lipohyalinosis, a lipid-rich, destructive process associated with very severe hypertension (>220 mm Hg systolic). In 5 of the 25 lacunes, the artery supplying the lacune appeared to be essentially normal and fully patent, a finding consistent with microembolism. The riddle of the nature and cause of lacunes had been solved.

Other Projects

Beginning in 1959 surgical carotid endarterectomy was performed at the MGH with increasing frequency in patients with TIAs. It was also performed as an emergency in the early stages of a progressing stroke despite advice to the contrary. In determining the degree of carotid stenosis, we used the diameter of the residual lumen as seen in the carotid angiogram rather than the percentage of occlusion, using the diameter of the ICA distal to the lesion as the denominator. The carotid endarterectomy specimens were routinely placed in formalin for fixation, without sectioning by the surgeon. After fixation, each was serially sectioned in its entirety at a thickness of 8 \(\mu\)m. In all, some 160 specimens...
were studied. This made possible unequalled visualization of all aspects of the atheromatous plaque, hemorrhage into plaque, small mural thrombus, ulceration, superimposed "rat-tail" thrombi, and the occlusive thrombus. Cases were operated on at different clinical stages—TIAs, thrombosis-involution, arteriogenic embolism, completed stroke, and asymptomatic. It was our conclusion that this was the only method of study that allowed the clinician to gain an adequate concept of the carotid thrombotic process. Analysis of the data supported failure of flow rather than embolism as the mechanism of TIAs. For those using carotid stenting, these studies provide a glimpse of the lesion being compressed.

Dr. Adams and I undertook a study of the effect of high blood pressure on the severity and morphology of atherosclerosis of the cerebral arteries as disclosed at postmortem examination. The cases were divided into 4 categories: hypertension with and without atherosclerosis and normal blood pressure with and without atherosclerosis. It turned out that there were no cases that qualified for the category of atherosclerosis with normal blood pressure. The obvious conclusion was that in the presence of normal blood pressure, atherosclerosis does not develop in the cerebral arteries. The same rule holds for almost all lacunes. The crucial importance of treating high blood pressure was clear: no high blood pressure, no hemorrhage.

In 1971 Dr. Robert Ojemann operated on a patient with a carotid stroke. An endarterectomy was unsuccessful, and in an attempt at restoring patency of the artery, the proximal 2 cm of the ICA were resected and the continuity restored by the insertion of an arterial graft. The resected specimen was sent for routine serial sectioning, which showed the appearance of a dissection, including the site of penetration through the intima. No cause for the dissection was evident. The sparse literature on spontaneous dissection of the ICA revealed only 9 clinical cases, 7 of which had been fatal. Three of the reported cases included illustrations of the respective carotid angiograms, which showed the ICA lumen greatly narrowed over a distance of several centimeters. Dr. Ojemann’s case had a similar angiographic appearance. The term "string sign" was suggested for the distinctive appearance. Within 24 hours, a colleague asked that I review a carotid angiogram of unusual appearance. This was done immediately, and the picture was that of a string sign. Later in the day, that patient’s ICA was explored, revealing an enlarged blue ICA with blood in the adventitial sheath. Thus, within 24 hours the pathology of dissection had been demonstrated and a clinical sign suggested, which was validated in another surgically confirmed dissection. In a matter of weeks, spontaneous dissection of the ICA was no longer regarded as a rarity. The clinical picture proved to be highly distinctive. In the following year, dissection of the ICA-MCA intracranially and of the VA in the neck was recognized, largely on the basis of the string sign.

Another topic of interest in the 1970s was ruptured saccular aneurysm. A comprehensive account of the clinical manifestations of subarachnoid hemorrhage was reported. The manifestations of cerebral vasospasm seemed to defy clinical interpretation, as many factors appeared to act in concert. When it was noted that angiographically demonstrated vasospasm did not occur in the first 72 hours after aneurysmal rupture, clinical events occurring in the first 72 hours could be set aside as unrelated to vasospasm. When only clinical events that had developed after 72 hours were included, it became clear that a 1:1 relationship existed between the presence of severe vasospasm and the occurrence of post-aneurysmal-rupture complications. Clearly, vasospasm was the guilty agent and had to be addressed.

With the improved CT imaging of the late 1970s, it became possible to assess the amount and localization of subarachnoid blood associated with ruptured saccular aneurysm. When the degree and site of vasospasm visualized on angiography was compared with the distribution of subarachnoid blood seen on CT, it became almost certain that the severity and site of vasospasm were directly related to the thickness of the local deposit of subarachnoid blood. The mechanism of vasospasm that had been regarded as multifaceted appeared to have a predominantly single cause. It became possible to predict the occurrence of vasospasm and even operate in the first few days to remove the subarachnoid clot and prevent vasospasm.

This account has not reflected clearly enough the importance that serial sectioning may have. Its usefulness was evident in several pathological processes described herein, particularly lacunar infarction. I have found the technique particularly useful in the study of cerebral vasculature.
invaluable in visualizing the essential details of a 3-dimensional disease process in their entirety. The method clarifies, thereby enabling more reliable speculation. Accurate visualization is the foundation of all new concepts.

To see ICA and BA thromboses in all their details provides ideas about the process and curtails erroneous thinking. Events at the site of rupture of a saccular aneurysm are largely conjectural. Serial sectioning of a block of tissue enclosing an undissected ruptured aneurysm revealed that the rupture had occurred at the base of the aneurysm, not the dome. The tiny site of rupture was inconsistent with the impression of "bursting." The mechanism of hemostasis could be inferred. The actual site of bleeding in amyloid angiopathy was revealed when a block of cerebral tissue enclosing a hemorrhage was blindly sectioned serially in its entirety. The disruption of the amyloid arterial wall was seen in detail. With the same technique, the details at the site of origin of a hypertensive hemorrhage were visualized. The mechanism of Duret hemorrhages remained uncertain until serial sectioning showed that the small arteries had lost their continuity. The ends of the disrupted arteries lay about 1 mm apart at the centers of small collections of extravasated red cells. I have found serial sectioning highly contributory.

I have frequently been asked about any special rules of procedure used in day-to-day work. There are none that have been recognized. Is it a matter of striving? Not really, for in retrospect it seems to have been effortless. Almost certainly, the backbone of my endeavor has been a knowledge of retrospect it seems to have been effortless. Almost certainly, procedure used in day-to-day work. There are none that have found serial sectioning highly contributory.

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