Carotid Endarterectomy: A Saga of Clinical Science, Personalities, and Evolving Technology

The Willis Lecture

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Mr Chairman, members, and guests of this annual international meeting on stroke, sponsored by the Stroke Council of the American Heart Association, an organization to which I have devoted over 20 years of admiration and service, it is an honor and privilege to present the Willis Lecture for 1998.

Sir Charles Willis published the *Anatome of the Brain and Nerves* over 300 years ago. Feindel edited an excellent compilation of Willis’ work and published his tercentenary edition, entitled *Cerebri Anatome*, in 1964. Willis’ publication was more than anatomy of the brain and nerves. It set forth a number of functional as well as anatomic descriptions of the brain and the cranial nerves. The most significant point of the work was the description of the functional anatomy of the cerebral circulation. Willis applied, for the first time, the knowledge of William Harvey’s brilliant discovery to the special problems of the blood supply to the brain. He gave the anatomic description of the arterial circle at the base of the brain. He recognized the significance of this unique vascular anastomosis. He supported his insight into the principle of collateral circulation to the brain by the intravascular injection of colored dyes and by ligation, in animals, of blood vessels supplying and draining the brain. Finally, he attempted to correlate the problems presented in his medical practice in light of these anatomic and experimental results often supported by autopsy observations. Clearly, he recognized that the carotid and vertebral arteries in the neck were the source of the blood supply to the brain and were integral to the cross-circulation described.

It is, therefore, highly appropriate that we focus today on the most commonly performed arterial surgical procedure, carotid endarterectomy, and the circuitous road of critique and clinical study it has followed to become the best evidence-based surgical procedure for the prevention of occlusive stroke.2,3

In preparing this lecture, I realized that beginning as a resident in neurosurgery under the tutelage of Francis Murphey and throughout my surgical and academic career, I had been involved in all of the National Institutes of Health studies of carotid endarterectomy. This involvement included the painful task of filling out forms for the Joint Study on Extradural Arterial Occlusive Disease and subsequent participation on the executive committees of the remaining studies, namely, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Arteriosclerotic Study (ACAS).2,3 I have always functioned as a supportive member of clinical investigation in the field of stroke, and although I was not a principal investigator, my keen interest and participation are record. During this 43-year period, I have known most of the personalities involved in critique, formulation, and grant politics; as participants of clinical studies from the Joint Study on Extracranial Occlusive Disease to surgical audits of endarterectomy, the devoted, competitive collaboration of neurologists and surgeons is legend.4,5 Finally, the 2 major studies of symptomatic and asymptomatic disease are very rewarding to our patients and all clinical investigators in the field of stroke. Hopefully, the moderate symptomatic stenosis group to be reported by Dr Barnett will conclude the clinical study of open surgical endarterectomy.

These studies, sponsored by the National Institutes of Health and in particular the National Institute of Neurological Disorders and Stroke, have been well planned, carried out by very experienced and devoted principal investigators, and, together with the first study on extradural vascular disease, constitute the greatest single expenditure of money and effort in the field of neurology to better the treatment of occlusive cerebrovascular disease. The studies have appropriately involved neurologists and surgeons with uncommon zeal for achievement and a rabidly competitive nature. The players favored hardball. Supporting, advising, and stimulating these studies has been the effort of a devoted neurological institute staff, namely, Murray Goldstein, Michael Walker, John Marler, and, lately, Zack Hall. Their patience, understanding, and devoted monitoring of the studies have produced excellent research results. All of the NINDS staff who have supported clinical stroke research deserve our thanks and admiration.

History

A historical review of carotid endarterectomy emphasizes there are very few new contributions but many refinements.
Chiari in 1906 and Hunt in 1914 stressed the importance of autopsy examination of the carotid arteries in the neck in patients who had cerebral infarctions. Hunt particularly noted that when no obstruction of an artery was found intracranially, the probable lesion was in the cervical carotid artery. These observations received little attention until 1951, when Miller Fisher, whose contributions are legend, reported artery occlusion and suggested this was a significant cause of cerebral infarction. His report emphasized that thrombosis was often superimposed on a gradual increase in subintimal atheroma in the internal carotid artery at the bifurcation in the neck. Fragments of the thrombus could break away and produce emboli to the more distal intracranial portions of the arterial circulation. He suggested the possibility for arterial reconstruction to reestablish flow and remove the atheroma. At the same time, cerebral arteriography was beginning to be applied to the study of occlusive vascular disease. Surgeons recognized early on that this definitive visualization of the cerebral arteries was absolutely essential in the investigation of occlusive vascular disease to seek the etiology producing the stroke and to determine which patients had surgically correctable lesions. Neurologists were critical and slow to accept angiography. Early attempts at reconstruction of the carotid artery at the bifurcation were carried out by Carrea, Molins, and Murphy in October of 1951 and subsequently by Eastcott, Pickering, and Robb in 1954. These early surgical procedures were not endarterectomies. Eastcott’s case involved the resection of a partially thrombosed segment of the common and internal carotid arteries and a reconstruction of the vessels by direct anastomosis. The procedure stopped further episodes of transient ischemic attacks (TIAs) in the patient. This is considered a landmark contribution. The operation on May 19, 1953, was witnessed by cerebrovascular surgeons, and according to Fields, Eastcott remembers that Jack Wiley of San Francisco suggested an endarterectomy should be considered for the treatment of this lesion (Reference 11 and W.S. Fields, personal communication, January 1998). George Dunlop, who photographed the procedure, subsequently loaned his slides to Jesse Thompson, who became one of the great spokesmen/surgeons reporting early excellent results for carotid endarterectomy in symptomatic and asymptomatic patients. Dr Michael DeBakey was also present. DeBakey’s monumental contributions to arterial surgery escalated. In 1965 DeBakey reported that he had operated on a patient on August 7, 1953, with thromboendarterectomy. This report supported his claim to having performed the first carotid endarterectomy. Although not published, there is controversy about this claim. Both William Fields, a neurological colleague of DeBakey, and the late George Enni, who worked in the Methodist Hospital in Houston, stated that a search of the records did not confirm that this was the first carotid endarterectomy, as reported (W.S. Fields, personal communication, January 1998). Fields credited the development of thromboendarterectomy as applied to the carotid artery to the late Dr Stanley Crawford. Denton Cooley used the first intravascular shunt at the time of endarterectomy. Clearly, the Houston group under DeBakey were the leaders of this aggressive approach to extracranial atherosclerotic occlusive disease. They not only demonstrated increasingly fascinating techniques of bypass and endarterectomy but also urged the use of arch aortography and later selective angiography of the extracranial vessels to diagnose the exact location of the areas of stenotic disease and demonstrated the incredible resilience of the circulation of the brain. Although others recognized the arteriographic ancillary and collateral pathways of the brain, the most complete early atlas was that of Weibel and Fields in 1969. This atlas, based on the extensive angiographic experience in Houston, attempted to describe every collateral arterial pathway after carotid or vertebral occlusive disease. It included a beautiful demonstration of the subclavian steal, a lesion rarely associated with brain stem infarction.

Recognizing the need to demonstrate that surgery for extracranial disease was effective in preventing stroke, Dr Michael DeBakey called a meeting in January 1959 in Washington for the purpose of developing a cooperative study of cerebrovascular insufficiency. The principal goal of the study was to determine the efficacy of arterial reconstructive surgery for surgically accessible lesions in the arteries of the neck and upper portion of the thorax. Initially, there were 10 participating institutions in the study; this ultimately grew to 24. This innovative and pivotal study was largely funded by the Heart Institute in a series of grants between 1959 and 1973. However, the Neurological Institute did participate in an advisory function. The executive committee consisted of John Sterling Meyer, chairman; William Fields, vice chairman; Raymond Bauer, secretary; and William Blaisdell, Stanley Crawford, Garber Galbraith, William Hass, Albert Heyman, Francis Murphey, Joseph Ransohoff, Richard Remington, and Edwin Wiley. This was an excellent mix of neurologists, vascular surgeons, and neurological surgeons. The study registry was directed by William Fields. Indeed, this study served as a model for all subsequent studies on cerebrovascular occlusive disease, particularly those with a surgical arm. William Fields deserves the thanks and respect from all neurologists and surgeons interested in occlusive disease for his tenacity and repeated practical contributions resulting from this study. The necessity of arteriography in evaluating patients with TIAs or strokes was proved. This technique afforded the evaluation and improved the selection of patients. It stimulated technological improvement of surgical technique. Eighty percent of nearly 5000 patients had complete 4-vessel examination arteriographically. The overall grave complication rate of arteriography was 1.2%. After 10 months into the study, the investigators agreed to randomize patients to surgery versus nonsurgical treatment. At this point, according to Fields, Dr DeBakey withdrew from the study. He was convinced that surgical treatment in his experience was definitive. The study was reported in 10 separate articles in the Journal of the American Medical Association, from March 1968 through June 1976. Of great interest to me, particularly emphasized in report IV by William Blaisdell, was the surgical mortality of 4.5% in 2400 operations. In addition, the study emphasized characteristics of the surgical lesion, including ulceration. For the first time, the study delineated careful methods of measuring common carotid and internal carotid and vertebral artery stenosis. The internal carotid artery was measured first at the level of the most marked stenosis, and
this in turn was compared with the lumen above the stenosis in a normal-appearing segment of the artery beyond the dilated carotid bulb. Although this technique was refined, it appears to be identical to the subsequent technique utilized by NASCET. ACAS! used this technique of measurement from its inception. The joint study! suggests almost every rational indication for carotid endarterectomy. The upper level of ready surgical accessibility as well as the contraindications to the operation were identified. These efforts further stimulated Francis Murphey, my chief, to contribute to the surgical treatment of occlusive vascular disease. He had returned from a meeting in 1956 stating that we had found not only a procedure that might prevent stroke but also a surgical procedure that was more efficacious, clinically rewarding, and technically easier than craniotomy for glioblastoma. Sadly, this is still true today.

Pritz’s recent publication! concerning the timing of endarterectomy after stroke assists surgical decision timing by the addition of CT scanning. In the cooperative study, early surgery was recognized as a cause of cerebral hemorrhage or infarct extension, particularly when the patient had a fixed neurological deficit or was obtunded or comatose. This study first recommended delaying surgery for 3 to 6 weeks after the last neurological event. Pritz’s study emphasized that patients with a stable acute stroke (neurological deficit lasting longer than 24 hours, a normal CT scan, and a normal level of consciousness) could probably undergo carotid endarterectomy shortly after diagnosis was made. The risk of stroke in this circumstance would seem to be approximately that of patients who have suffered a TIA. Patients with a low density on CT scan without significant shift, stable neurological deficit, and a normal level of consciousness have been reported to undergo early surgery with low risk. Patients who have a brain shift on CT with a normal level of consciousness are probably at an indeterminately increased risk for complications of endarterectomy performed early. Stroke patients who have a depressed level of consciousness presumably due to increased intracranial pressure and a probable significant shift of structures on CT are not surgical candidates. Throughout the joint study numerous technical advances were made and surgical experience gathered. Surgical mortality decreased from 5.1% in the first 4 years to 1.5% later in the study. Additionally, myocardial infarction was identified as the principal cause of late mortality in those patients undergoing successful surgical treatment. Providing the patients survived the surgical therapy, the occurrence of new stroke was 4% in the surgical group and 12.4% in the nonsurgical group. Nevertheless, this study was not definitive for demonstrating the superiority of surgical treatment to medical therapy, and numerous criticisms emphasizing the need for definitive studies followed, for example, those of Jonas and Hass, J.P. Mohr, and Whisnant et al. Concomitantly, further refinements in stroke diagnosis evolved, including the significance of cardiac causes of stroke and proven medical therapies. Millikan and Whisnant proclaimed and explained the further significance of TIAs and were proponents of anticoagulant therapy. Fields and Barnett proved that platelet inhibition with aspirin reduced further stroke risk in over 20% in patients who had sustained stroke or TIA. Indeed, the collaboration of aspirin inhibition trialists at Oxford continues to validate aspirin as preventive and therapeutic in atherosclerotic disease of the brain and heart. Despite criticism, the surgical procedure became extremely popular, and excellent results were related by the champions of the procedure, eg, Crawford, Robertson, Thompson, Sundt, Wylie, Murphey, and others. Lengthy discussions were related by the leaders of the procedure, eg, Crawford, Robertson, Thompson, Sundt, Wylie, Murphey, and others.

Two years later, at the 15th Princeton Conference in St Louis led by William Powers and Marcus Raichle, Hachinski reported that the London, Ontario, group had submitted a proposal for a North American symptomatic endarterectomy study to the NINDS a week prior to the meeting. Jim Toole announced a proposed asymptomatic carotid endarter-
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initially not well received but was literally kept alive by

Respecting the neurological concerns for audit, William Fields suggested that this Stroke Council establish a commit-
tee to put forth the accepted mortality and morbidity for carotid endarterectomy and the need for surgical audit. This was achieved and published. Until the results of the symp-
tomatic and asymptomatic trials became known, it was a position statement of considerable influence in patient selec-
tion and surgical performance. The proposed morbidity and mortality figures were supported by the final result of the trials.

Murray Goldstein recently stated that he became interested in the need for carotid endarterectomy trials not only by the literature that I have briefly cited but also by the fact that a number of inquiries were received by the Neurological Institute concerning the procedure (M. Goldstein, personal communication, January 1998). He suggested to Barnett, who had just completed the Extracranial/Intracranial Bypass Study, that a symptomatic trial was indicated and a grant of surgical versus medical therapy would be well received. Barnett undertook the necessary preplanning to meet with the staff at the Neurological Institute in the preparation of his grant. Simultaneously, Jim Toole initiated preliminary work on a project to evaluate asymptomatic significant carotid artery stenosis versus best medical treatment. Initially, this study involved proposals to determine the rate of progression of stenosis and the instance of concomitant coronary disease as well as surgical versus medical therapy of asymptomatic carotid artery stenosis. Wes Moore and I were early partici-

Eventually the 2 trials were funded. It is important to understand the policy of the then-director of the NINDS, Dr Murray Goldstein, at the time these investigator-initiated grants were funded. Unlike the Heart Institute and its con-
tracts, the Neurological Institute urged grant application and the funding of specific qualified, sensitive scientists to manage the grants appropriately. He initiated the establish-
ment of a monitoring committee or a data and safety monitoring committee so that the activity of the grant, as well as the results and the rate of recruitment, could be monitored fiscally. Since this committee was established for fiscal as well as study responsibility, it was appropriate that it could be

The patients in NASCET were required to undergo angiogra-
phy, whereas in ACAS the patients were selected and screen-
ed by Doppler evaluation or arteriography. Meticulous attention was paid to quality control in the ACAS study, since Doppler evaluation was being used. By careful standardiza-
tion of Doppler machines with controlled angiograms, thresh-
olds at each center for detecting hemodynamically significant stenosis were obtained. These thresholds were carefully monitored throughout the study, and subsequent analysis revealed that the actual positive predictive value of the Doppler screening was 93%, indicating that the medical patients did indeed have significant carotid artery stenosis, with fewer than 5% having less than the required 60%. The rigor of using Doppler evaluation on an ongoing basis was extremely difficult, particularly since during the time of the study, technological improvement in noninvasive screening of carotid stenosis was exploding. The quality of data handling and management in ACAS were superb.

Simultaneously, NASCET and the European Carotid Sur-
gery Trial reached the same early conclusion. Accordingly, the NASCET trial was stopped by the Data and Safety Monitoring Committee because the surgical procedure was shown to be highly beneficial to patients with recent hemi-
spheric and retinal TIAs or nondisabling strokes and ipsilat-
eral high-grade stenosis (70% to 99%) of the internal carotid artery, an early result no one had envisioned. This resulted in an announcement in February of 1991, and the information was subsequently disseminated widely. The ultimate result was reported in the August 1991 issue of the New England Journal of Medicine. Patients with <70% symptomatic carotid stenosis continued to be studied to determine whether the moderate grades of stenosis should be best treated by medical or surgical therapy. Despite the excellent results reported by NASCET in the patients who had symptomatic carotid stenosis of ≥70%, a member of the Data and Safety Monitoring Committee of NASCET wrote a highly critical editorial.

ACAS ultimately included patients from 39 clinical sites across the United States and Canada. Between December 1987 and December 1993, a total of 1662 patients with asymptomatic carotid artery stenosis of ≥60% were random-
ized. The analysis used follow-up data on 1659 of these patients. Medical therapy in both the symptomatic and the asymptomatic trials employed the use of aspirin and medical risk factor management. After a median follow-up of 2.7 years, with 4657 years of patient observation, the aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was estimated to be 5.1% for the surgical patients and 11% for patients treated medically. The data were particularly strong for men, and it was concluded that patients with asymptomatic carotid stenosis of ≥60% in diameter, whose general health made them good candidates for elective surgery, would have a reduced 5-year risk of ipsilateral stroke if endarterectomy was performed with <3% perioperative morbidity and mortality. Previous to this publication, in May 1995 the results of the Veterans Affairs Trial demonstrated that endarterectomy was preferable to
medical management for preventing TIA in asymptomatic carotid stenosis. This report was criticized in an editorial in the same journal by Barnett and Haines. The CASANOVA trial did not include stenosis exceeding 90%. The Mayo Clinic trial was terminated early because of excessive cardiac events. However, it did emphasize that the use of aspirin throughout the perioperative period and beyond in patients with asymptomatic carotid stenosis who undergo carotid endarterectomy was probably very efficacious.

In the ACAS study initially TIA or cerebral infarction occurring in the distribution of the study artery and any TIA, stroke, or death occurring in the perioperative period were the end points. However, in March 1993, the primary outcome measures were changed to cerebral infarction occurring in the distribution of the study artery or any stroke or death occurring in the perioperative period. In my opinion, this change made the results of the asymptomatic carotid trial more clinically significant. Subsequent to this report, Barnett and Haines, and others have criticized the results and still remain unconvinced that carotid endarterectomy for asymptomatic patients with hemodynamically significant stenosis is best treated by surgery. Are these critics attempting to state that the results of the trial are not generalizable or valid?

The conclusions of the trial and subsequent publication by the surgeons involved in the asymptomatic carotid trial emphasize that, providing the surgical morbidity and mortality for endarterectomy is <3% and the patients are selected according to the criteria utilized for study entry and subsequently managed medically with the use of aspirin therapy, the procedure clearly is of benefit in reducing stroke compared with medical therapy alone. At the same time, it could be argued the results from the symptomatic trial are not generalizable unless the surgical morbidity and mortality rate is <6% and the patients are selected medically and according to the requirements of the trial. I am convinced that surgical therapy has been established in both the symptomatic and asymptomatic groups for hemodynamically significant carotid stenosis. In fact, in 1995, 132,000 endarterectomies were performed at a cost of over a billion dollars in the United States (M. Walker, personal communication, February 1998).

Interventional Neuroradiology

New technology for dealing with carotid and vertebral stenotic lesions that are symptomatic and asymptomatic has appeared in the field of interventional neuroradiology and cardiology. It has been possible with the development of excellent small catheters that can be placed through the lesion, with balloons that can be used to dilate the lesion, and with stents that can be placed to prevent restenosis. The patient is usually maintained on anticoagulation, and the results that are being reported are certainly worthy of our consideration. Fisher and Jordan, from the University of Alabama, report that the results of the surgical treatment versus angioplasty regarding serious stroke or death appear to be about identical in the 2 series of patients (W.S. Fisher III, W.D. Jordan, unpublished data, 1997). On the other hand, with angioplasty there is a 6-fold increase in the incidence of so-called small strokes. The procedure appears to be indicated in certain high-risk patients who require endarterectomy, or in lesions that are above the mandibular mastoid line, or in the presence of restenosis or radiation stenosis, or with carotid dissection. Robert Ferguson of our center has performed carotid angioplasty for 11 years. He met with the executive committee of the ACAS study in 1991 in Dallas to put forth the idea that a prospective study on angioplasty versus endarterectomy should be done. Subsequently collaborating with Robert Hobson and others, they submitted a grant to the National Heart, Lung, and Blood Institute that was subsequently referred to the NINDS. Henry Barnett became intensely interested in prospectively investigating whether angioplasty with stenting was worthy of study. The ideas were tested in a formative meeting in early 1996. A grant very similar to that of the Hobson and Ferguson group was prepared. There was some reluctance at the NINDS to accept and fund such costly proposals, but this was resolved through stringent persuasion. The 2 grants were received by the NINDS in early 1997 and underwent a special panel review in early September 1997; neither received priority scores low enough for funding. It was the recommendation of the panel that the 2 groups proceed with a collaborative grant to look prospectively at carotid artery angioplasty with stenting versus surgical endarterectomy. The Hobson-Ferguson group is called the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), and the Barnett (and now Barnett-Easton) group is the Carotid Artery Stenting Endarterectomy Trial (CASET). Both groups are looking prospectively at endarterectomy versus the angioplasty technique.

At the present time, Dr Easton is principal investigator of the CASET study and Dr. Hobson is principal investigator of the CREST study. It may be that 2 separate, competitive applications will again be submitted to the NINDS.

Many stroke therapists are in favor of a trial to test angioplasty against evidence-based endarterectomy (References 45 through 48). W.S. Fisher III, W.D. Jordan, unpublished data, 1997. Meanwhile, angioplasty is here to stay!

The American Heart Association recognizes the seriousness of the changing technology and has reflected this concern in a recent scientific advisory entitled, “Carotid Stenting and Angioplasty.” This was prepared by an eminent group of neurologists, radiologists, neurosurgeons, and representatives from cardiac and vascular surgery, epidemiology and prevention, and clinical cardiology. They recognize the popularity of the procedure but at the same time point out that the procedure is unproved. The benefit of carotid endarterectomy in symptomatic patients has been convincingly demonstrated. In addition, the complication rates have been well defined and appear to be acceptably low in the hands of experienced surgeons. In addition, although angioplasty and stenting are less invasive than surgery, the risk of diagnostic carotid angiography alone, with its attendant catheter manipulation, are not trivial. Clearly, before carotid percutaneous transluminal angioplasty and stenting can be considered for wide use, morbidity and mortality rates must be clearly defined. In addition, acute occlusion of the
carotid artery may not be amenable to emergency surgical correction and does occur during angioplasty. At a minimum, the equivalence of percutaneous approaches to surgical carotid endarterectomy must be established in sufficiently powered, prospective, randomized trials. The consensus at this point is that carotid angioplasty and carotid stenting, with rare and infrequent exceptions, should be undertaken only as part of a prospective, randomized trial with “independent dispassionate oversight.”

Trials are clearly recommended to resolve this problem. Insistence on randomized trials will allow comparison of a new technology with a well-established “gold standard” of carotid endarterectomy. The writers appropriately state “use of the technology because it and the patient it is to benefit exist, is not at this point justified or justifiable.” Hopefully, prospective studies will be forthcoming, and if new competition for funding rather than cooperative collaboration is required, so be it.

Alas, carotid endarterectomy, the saga continues . . .

References


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