Historical Account of Interventional Neuroradiology

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109.1 Introduction

Interventional neuroradiology draws upon a rich and diverse practitioner base. Significant contributions have been and continue to be made by specialists in radiology, neurosurgery, neurology, cardiology, vascular surgery, and other disciplines. Its level of technical sophistication, conceptual approach, and continuous rapid development, however, maintain its integrity from its individual kindred specialties. Uniquely designed catheters, wires, embolic material, and micro-engineered devices provide access and interventions for incredibly remote vascular pathology, guided in real time by continuous imaging feedback along otherwise invisible internal paths. Such qualities place interventional neuroradiology at the top among the most minimally invasive neurosurgical interventions available today. Of course, its beginnings were more rudimentary than its current form of practice would suggest. In this chapter, we trace the history of interventional neuroradiology by describing the most pivotal contributions, from its early days as an extension of open neurosurgical methods and its evolution from diagnostic angiography.

The history of interventional neuroradiology is reviewed beginning with the development of cerebral angiography. Early angiographic procedures were performed by open surgical exposure of the cervical vessels, with a gradual transition to the transfemoral route with the introduction of the Seldinger technique and the advent of flexible, steerable microcatheters made from polyethylene and silicone. Nonselective embolization offered an effective therapy for unresectable arteriovenous malformations (AVMs), but off-target embolization and infarction of normal parenchyma was a major issue. Safer, more effective, selective therapies for vascular lesions developed at a more rapid pace in the 1970s and the 1980s following the introduction of Serbinenko's flow-guided detachable balloon. Detachable balloons were widely used for many years, but were eventually replaced with liquid embolics and the Guglielmi detachable coil, which opened up a new era in endovascular therapy for vascular malformations and aneurysms. Modifications to Guglielmi's bare platinum coil and implementation of balloon- and stent-assisted coiling were borne out of necessity for safe endovascular interventions to treat wide-necked, fusiform, and complex aneurysms and to minimize recanalization rates. Balloon angioplasty and stenting to treat extracranial atherosclerotic stenosis were largely an extension of percutaneous coronary artery interventions. Early studies comparing angioplasty and stenting to the gold standard, carotid endarterectomy, favored the endovascular approach, but the most recent data are somewhat less promising. Treating intracranial stenosis by angioplasty and stenting has required adaptation of these tools to the delicateness and idiosyncrasies of the cerebrovasculature. Such technological achievements have enabled the relatively recent advancements in endovascular therapy for acute stroke.

109.2 Cerebral Angiography and Contrast Media

Cerebral angiography forms the foundation of interventional neuroradiology. The early development of angiography quickly followed the creation of the first radiograph in 1895 by German physicist Wilhelm Conrad Roentgen. Within months of this achievement, in Vienna, Eduard Haschek and Otto Lindenthal demonstrated the radiographic visualization of cadaveric peripheral blood vessels with injection of radiopaque solutions.

The first cerebral arteriograms were performed in 1927 by the multitalented Portuguese neurologist Antonio Caetano de Abreu Freire Egas Moniz, whose life accomplishments included the Nobel Prize in Physiology or Medicine, which he shared in 1949 for his efforts related to the neurosurgical operation of frontal leucotomy for treatment of psychiatric conditions. Moniz developed the technique of arteriography on dogs in 1926 using a solution of strontium and lithium bromide as an intravascular contrast medium. This was similar to the prior work of Berberich and Hirsch in Germany in 1923, but Moniz followed up his preliminary canine studies with cerebral arteriograms in human cadavers and subsequently in living patients in early 1927 [1]. Radiopaque contrast medium was delivered directly into the surgically exposed common carotid artery. With minimal modification, this was essentially the way cerebral arteriography was performed for the next three decades.

Moniz presented arteriography as a safer alternative for tumor localization than the prevailing neuroimaging modality of that time, ventriculography. Ventriculography was a technique conceived

and developed in 1918 by American neurosurgeon Walter Dandy and involved the replacement of cerebrospinal fluid with air injected directly into the ventricular system. Despite the risks inherent to ventriculography, it was not supplanted by arterial encephalography, which was deemed an inferior alternative for diagnosing tumors by mass effect, but an excellent modality for diagnosing cerebrovascular pathology. For this purpose, cerebral angiography was widely adopted around Europe during the 1930s, shortly after its introduction.

Despite its popularity in Europe, cerebral angiography was late to catch on in the USA for two main reasons: first was the histological toxicity of the thorium dioxide contrast agent being used in Europe and second was the minor surgery involved in exposing and cannulating the common carotid artery. The latter issue is addressed further later in this chapter (see ▶ Sect. 109.3). Regarding the former issue, a contrast medium should ideally meet the following four criteria, as described by Morgan and Roach in 1950 in the *American Journal of Medical Science*: It should be (1) innocuous to the patient, (2) rapidly and entirely eliminated from the body, (3) radiopaque enough to provide adequate contrast relative to surrounding parenchyma and bone, and (4) readily miscible with blood so as not to create artificial filling defects that could mimic endoluminal lesions. Moniz experimented with several compounds containing halides, including aqueous solutions of strontium bromide and subsequently sodium iodide. (These agents are highly attenuating to x-rays due to their high atomic number, and are therefore good for providing radiographic contrast.) He ultimately abandoned both of these media due to their serious adverse reactions, settling upon a colloid of thorium dioxide, known by its trade name Thorotrast [2], the use of which he described in the literature in 1931. Although not typically associated with immediate adverse reactions, thorium dioxide is radioactive and moreover remains in the body permanently, sequestered by the reticuloendothelial system, where it can cause tissue necrosis and sarcogenesis. Despite its documented histological toxicity, Thorotrast remained in regular use throughout Europe. Because of its poor safety profile, however, its use was rejected by the American Medical Association in 1932, further delaying the assimilation of cerebral angiography into North American medical practice.

In 1939, the iodine-based aqueous contrast agent Diodrast (3,5-diiodo-4-pyridon-*N*-acetic acid diethanolamine) was introduced for use in cerebral angiography. The properties of Diodrast were already known since it had been in use for some time, mainly for intravenous pyelography. Although local and systemic reactions were reported with its use, even more frequently than with the use of Thorotrast, Diodrast was felt to be relatively safe in the quantities injected for cerebral angiography and was rapidly eliminated in its original form in the urine. Its application to cerebral angiography was first explored by several investigators working independently, namely J. Lawrence Pool and Sidney Gross, both at Columbia University Medical Center in New York, and Arne Torkildsen of the University Clinic in Oslo, Norway (◘ Fig. 109.1). By 1950, cerebral angiography was in fairly common use in academic institutions throughout the USA as well as in some community hospitals.

Conventional ionic contrast media were associated with significant subjective adverse effects such as pain, flushing, and nausea, as well as objective adverse effects including anaphylactic reactions, direct chemotoxic effects on erythrocytes and endothelium, and hemodynamic changes. These contrast media were used in high concentration in order to produce adequate radiographic density, and were therefore high in osmolality relative to plasma. High osmolality was believed to be responsible for the negative effects of these contrast media, and low-osmolality contrast media were developed primarily to address this issue. Metrizamide (Amipaque), introduced in 1972 by the company Nyegaard, was the first non-ionic, low-osmolality contrast medium. Metrizamide was expensive and inconvenient to use and was quickly replaced by iohexol (Omnipaque). The incidence of side effects significantly decreased with the use of the new non-ionic agents, but their apparent association with thromboembolic events became a subject of considerable debate. As a result, heparin may be added to iohexol for cerebral angiographic procedures.

109.3 Endovascular Access and the Seldinger Technique

A German surgeon named Werner Forssmann is credited with popularizing the use and multiple applications of catheter angiography. In 1929,

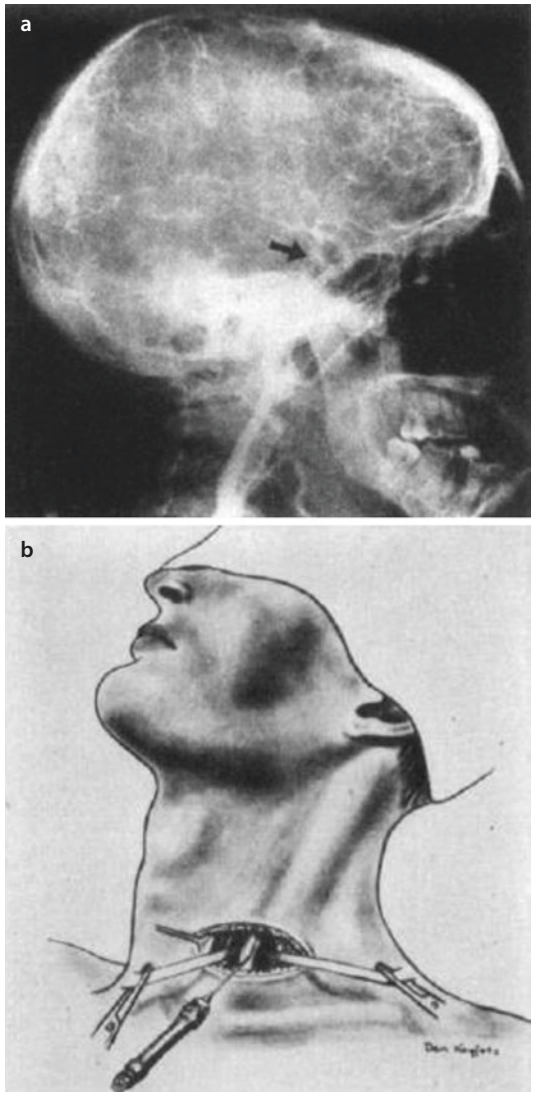

Fig. 109.1 **a** Cerebral arteriogram of a 43-year-old man performed circa 1941 with injection of 10 cc of 50% Diodrast into the right internal carotid artery (ICA). The arteriogram demonstrates an aneurysm (*arrow*) of the right ICA near the origin of the posterior communicating artery. The patient presented with acute right supraorbital pain and right cranial nerve III palsy. **b** Early cerebral angiograms were performed under local anesthesia by cannulation of a surgically exposed carotid artery and direct injection of contrast medium into the vessel. This method, or its percutaneous variation, was used into the 1950s, even after transfemoral catheterization and the Seldinger technique had been introduced (from Gross [2])

while in surgical training at August Victoria Home at Eberswalde near Berlin, Germany, Forssmann demonstrated, on himself, that a thin catheter inserted into the antecubital vein could reach the right atrium of the heart, which he proved radiographically. Although this was already known from animal studies, Forssmann had demonstrated the feasibility of safely carrying this out in humans, paving the way for cardiac catheterization and cardiovascular pathophysiologic evaluation. Together with two other pioneers in the field—Andre F. Cournard and Dickinson W. Richards of Columbia University Medical Center—he shared the Nobel Prize in Physiology or Medicine in 1956 for this contribution.

Despite Forssmann's successful demonstration, and the growing use of cerebral angiography, it was many years before catheter-based *intervention* began to develop. Cerebral arteriography in its original form required open surgical exposure and cannulation of the carotid artery into which contrast was then injected. The transition to percutaneous carotid injection, introduced in the USA in 1936 by Julius Loman and Abraham Myerson working at Boston State Hospital and in Japan in 1937 by Kentaro Shimidzu at Tokyo University Hospital, is considered a major accomplishment that helped promote cerebral angiography into general practice. In 1941, Pedro L. Fariñas of Havana, Cuba, demonstrated that transfemoral catheter access was feasible and associated with a lower rate of complication than direct carotid access; however, carotid stick remained in common use well into the 1950s. (In William Friedkin's horror movie, the *Exorcist*, filmed in New York, the demonized child played by Linda Blair underwent a direct carotid stick cerebral angiogram as recently as 1973.)

The catheterization technique introduced by Swedish radiologist Sven Ivar Seldinger in 1953 was a milestone not just for cerebral angiography but for interventional radiology in general. The Seldinger technique is so intuitive and simple, and now standard practice, for gaining arterial access in endovascular procedures, that one might easily overlook this major contribution if it did not bear the originator's name in common parlance. Seldinger's technique—puncture the blood vessel with a needle, insert a guidewire through the needle, remove the needle, insert a flexible catheter over the guidewire, remove the guidewire—was unique in its use of a flexible metal «leader» (i.e., guidewire) «with increased flexibility of its distal 3 cm» and a polyethylene «tube» (i.e., catheter) of the same diameter as the needle [3]. Importantly, Seldinger's innovative technique was made

possible by E. Converse Pierce's concurrent development of the flexible polyethylene catheter in 1951 at The Children's Medical Center in Boston.

109.4 Early Instrumentation and Interventions

109.4.1 Catheters

Early endovascular treatments may be best described as «transluminal,» or «endosaccular» in the case of aneurysms, as they typically involved an open surgical approach and direct puncture of the vessel. That began to change with the advent of catheters that were flexible, steerable, and long enough to reach distal intracranial arteries without causing significant vessel injury. This technique offered a safer and more effective method to perform embolization procedures than direct surgical exposure. In 1962, radiologist Charles Dotter at the University of Oregon in Portland introduced a flexible, flow-guided microcatheter made of soft silicone rubber, also known by its trade name, Silastic (Dow Corning Corporation, from the words «silicone» and «plastic»), intended for use in cardiac catheterization [4]. This invention soon came into widespread use in interventional neuroradiology.

Magnetically guided catheters for superselective vascular catheterization were developed in the 1960s based on the para-operational device (POD) designed by Ephraim Frei and colleagues in 1963. This ingenious methodology used either an external static magnetic field and field gradients or an alternating magnetic field to propel and steer a tiny magnetic particle, such as a magnetic catheter tip, intravascularly through tortuous arteries. The technology was further developed and reported in 1968 and 1969 by Shyam Yodh and colleagues at Massachusetts General Hospital, Sadek Hilal at Columbia University's Neurological Institute, and John Alksne at the University of California in Los Angeles in the hope of creating a better means of selective angiography.

The other intended application of magnetically guided catheters was the effective obliteration of vascular lesions by precise delivery of embolic material. The goal was to overcome the limitations of non-guided, non-selective delivery of embolic material into the proximal carotid artery demonstrated by Alfred Luessenhop and William Spence in 1960 [5]. Sadek Hilal and W. Jost Michelsen at Columbia University were among the first to present their results on the use of magnetically guided catheters for angiography in humans in 1968. In 1970, James A. Taren and Trygve O. Gabrielsen reported their successful treatment of unresectable extracranial facial AVMs in two patients using magnetic catheter guidance in the journal *Science*. Once the catheter was in the desired location, electric current was passed through the magnetic electrode tip of the catheter, causing radiofrequency-induced heating of the surrounding tissue and local thrombosis of the feeding arteries. Interest in magnetic catheter guidance eventually waned, however, as the goal of selective distal vascular access with microcatheters was never fully realized with this technology.

In 1973, Charles Kerber, a radiologist at the University of Oregon, developed a flow-guided calibrated-leak balloon catheter, which he described in the literature in 1976 [6]. The instrument consisted of a silicone catheter with a silicone balloon affixed to the end. When inflated, this balloon catheter allowed a small amount of contrast agent or liquid embolic material to escape into the bloodstream while the balloon remained inflated. On the other side of the continent, Paul H. Pevsner at the Medical College of Virginia independently developed an almost identical calibrated-leak balloon system around the same time as Kerber [7]. Kerber chose silicone rather than polyethylene because he felt that it provided superior flexibility and directional control and enabled him to achieve superselective catheterization of fourth- and fifth-order distal branches. The catheter also differed from previous flow-guided catheters in that it had a single lumen rather than two lumens (one for inflating a balloon, the other for injecting contrast or embolic material). By Poiseuille's relation, the resistance to flow of an injected solution was significantly reduced in the single-lumen catheter compared to that of double-lumen catheters. The problem with the calibrated-leak balloon was the potential for overinflation, which was associated with a high rate of vessel perforation.

In the 1960s, Russian neurosurgeon Fedor A. Serbinenko was developing an intracranial balloon catheter occlusion technique, which he reported in the Soviet medical literature in 1971 and subsequently in the English-language literature in 1974 [8]. Serbinenko described the use of

two types of inflatable, silicone balloons—one which was used only for occlusion and another which was occlusive but also had a separate lumen for bidirectional passage of liquids and contrast. These balloons allowed various diagnostic angiographic studies to be performed, including tests to determine collateral flow, evaluate temporary ischemia, and determine the blood supply to vascular malformations. Serbinenko's technique also allowed for both temporary and permanent therapeutic balloon occlusion, which he demonstrated successfully on cavernous carotid fistulas and cerebral aneurysms. Permanent occlusion was achieved by use of a detachable balloon that Serbinenko had also designed (Fig. 109.2).

Serbinenko's contributions have had a major impact on the field of endovascular neurosurgery, particularly the introduction of detachable balloons, upon which great advances have been made. The years that followed are considered by some to represent the beginning of the modern era of interventional neuroradiology led by the pioneering work of René Djindjian in Europe and Kerber and Pevsner in the USA.

Up to this point, the vascular catheters developed were of the flow-guided type. The other major type of catheter still in use today is the over-the-wire catheter. As the name suggests, these catheters are advanced over a steerable or torqueable guidewire and can therefore be mechanically directed into branch vessels. Early models, which appeared in the 1970s, were not popular or widely marketed and are poorly documented in the literature. The first widely marketed over-the-wire catheter system for cerebral vascular applications was the Tracker™ microcatheter and Microguide wire (Target Therapeutics, Fremont, CA, USA), introduced in 1986, which had a huge impact on the field. Today, a broad variety of over-the-wire microcatheters are available from several vendors, including those made of radio-opaque polyethylene, with advanced wire braiding and hydrophilic coatings, and a few that are compatible with the dimethyl sulfoxide (DMSO) solvent used with ethylene-vinyl alcohol embolic material.

The radiographic imaging equipment used to perform cerebral angiography and endovascular procedures usually receives little attention in historical accounts of these topics. Yet, it is a critical component in the evolution of interventional neuroradiology. In particular, digital road mapping was introduced in 1982 at the University of Pittsburgh and, like the Seldinger technique, is now universal in practice and easy to overlook in terms of its historical importance. The addition of road mapping to digital subtraction angiography (DSA) has made endovascular embolization safer, more effective, and lower in radiation exposure to patients and operating staff.

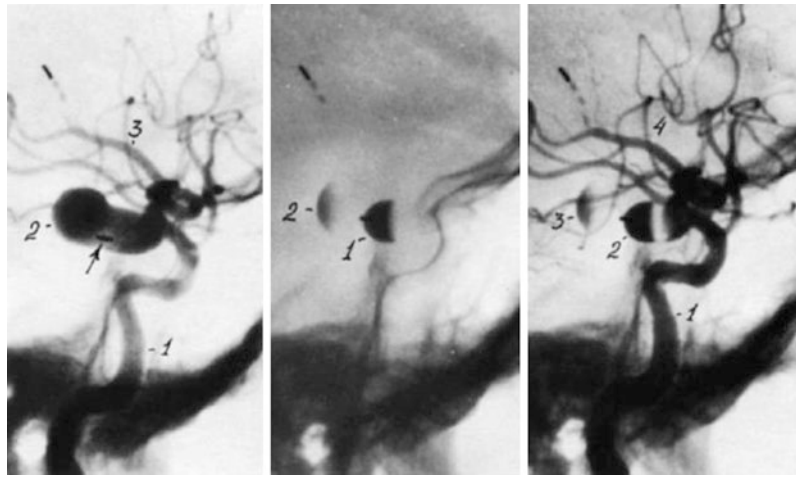

Fig. 109.2 Balloon occlusion of a supraclinoid internal carotid artery (ICA) aneurysm. (*Left*) Contrast-filled balloon (*arrow pointing to balloon marker*) in the aneurysm. *1* ICA, *2* aneurysm dome, *3* middle cerebral artery (MCA). (*Center*) Radiograph obtained after balloon positioned. *1* balloon, *2* aneurysm dome with residual contrast. (*Right*) Postoperative radiograph after catheter withdrawal. *1* ICA, *2* balloon, *3* aneurysm dome, *4* MCA (from Serbinenko [8])

109.4.2 Arteriovenous Malformations and Embolic Materials

Rare reports of attempted embolic therapies can be found in the literature from the early twentieth century. In 1904, Robert Dawbarn, a surgeon with New York Polyclinic, presented his «starvation plan» for head and neck tumors to the American Medical Association in which he injected an organic occlusive mixture consisting primarily of melted paraffin wax into a surgically exposed external carotid artery. Many years later in 1930, Barney Brooks used muscle to surgically embolize and close a cavernous carotid fistula.

It was not until 1960 that the first *endovascular* embolization of a cerebral AVM was performed by Luessenhop and Spence at Georgetown University Hospital [5]. Luessenhop's theory was based on the preferential flow towards the AVM, called the sump effect, caused by the increased blood flow, lower resistance, and hypertrophied arterial size of the AVM relative to the surrounding normal cerebral vasculature. That is, by following the high-flow, low-resistance, larger arteries leading to an AVM, properly sized embolic particles introduced proximally into the circulation would preferentially flow to the AVM nidus where the main afferent artery arborized into smaller vessels (Fig. 109.3). Luessenhop and Spence successfully tested their technique of «artificial embolization» on a 47-year-old woman with a symptomatic inoperable AVM of the left middle cerebral artery (MCA). Under local anesthesia, the left carotid bifurcation was exposed, and four spherical emboli of methyl methacrylate ranging from 2.5 to 4.2 mm in maximum diameter were injected successively from smallest to largest at 15-min intervals. In the days that followed, the patient suffered a transient ischemic event but ultimately recovered.

In 1964, Luessenhop and Velasquez constructed an irrigated external glass chamber, which they attached to the external carotid artery (ECA) and used to access the internal carotid artery (ICA) with a Silastic catheter. After experimenting with glass models of the ICA, then on cadavers, and finally perfecting their technique on dogs, they performed endovascular embolization on two patients with intracranial AVMs using a modification of their earlier technique. A small,

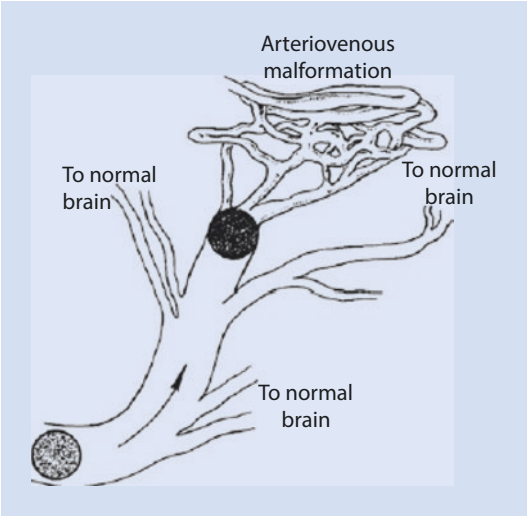

Fig. 109.3 This figure from Luessenhop and Spence [5] demonstrates Luessenhop's strategy for treating arteriovenous malformations (AVMs) with Silastic spheres by the «sump effect»

2.5-mm spherical Silastic pellet attached to the end of a silk suture was flow-guided towards the AVM. The suture allowed the pellet to be withdrawn if blood flow did not carry it to the desired location. Once in an acceptable position, the pellet was released by cutting the suture. The process was repeated multiple times to diminish flow.

Luessenhop and his colleagues went on to further evaluate and classify AVMs into various types based on their location and feeding vessel pattern, which was helpful in determining which AVMs were amenable to endovascular treatment. Embolization offered an alternative to the existing therapies for non-resectable AVMs, radiation, and arterial ligation, neither of which had been particularly successful. The main problem with non-selective embolization of AVMs was the diminution in the sump effect that occurred with progressive embolization, such that at some point in the procedure, the path of least resistance was no longer towards the AVM but along the normal branch vessels, resulting in off-target embolization and infarction of normal tissue. Advances in the application, efficacy, and safety of embolization were made in the 1970s by Djindjian at Hôpital Lariboisière in Paris, Irvin I. Kricheff at New York University Medical Center, Samuel M. Wolpert and Bennett M. Stein at Tufts-New England Medical Center in Boston, Hilal and Michelsen at Columbia University Medical

Center, and John L. Doppman and Giovanni Di Chiro at the National Institutes of Health. Contributions included new endovascular approaches, use of transfemoral catheterization, and embolization of spinal AVMs and ECA territory vascular malformations. In 1970, Roushdy Boulos, Irvin Kricheff, and Norman Chase at New York University Medical Center showed how cerebral angiography could be used to monitor the progression of non-selective embolization and determine a suitable stopping point to the procedure. Nevertheless, embolization of normal parenchyma remained a major problem without the ability to selectively catheterize and embolize the nidus of a cerebral AVM. Furthermore, it was eventually recognized that occlusion of the nidus of the AVM, not just the feeding arteries, was important for successful treatment.

Throughout the 1970s and the 1980s, others attempted iatrogenic embolization of AVMs using a variety of embolic materials, including polymer threads, silk sutures, gelatin particles, gelfoam, polyvinyl alcohol (PVA) foam and particles, and autologous clots. Off-target embolization, recanalization, and vasculitis secondary to the use of certain embolic materials remained potential problems. PVA particles, which are still in use today, show the ability to penetrate the AVM nidus, but recanalization can occur in 2–14 days. PVA is typically used for presurgical embolization of AVMs that will be resected within 1–2 days. Some studies have suggested that microspheres, hydrophilic beads made of an acrylic copolymer cross-linked with gelatin, achieve better small-vessel penetration than PVA, which may aggregate before penetrating the small vessels.

The development of flexible steerable over-the-wire and flow-directed microcatheters was a major technical advancement, offering at least a partial solution to the problem of off-target embolization that was seen with the non-selective embolization technique. Eliminating the problem completely was hampered by the inability of microcatheters to deliver an embolus of sufficient size to occlude the vessel of interest. Solidifying adhesives such as the cyanoacrylates, which were originally produced as a surgical suture replacement, showed particular promise in this regard, as these compounds could be injected through microcatheters as a liquid and form an occlusive mass in situ within the blood vessel. In 1972, Paul H. Zanetti and Frank E. Sherman of the University of Pittsburgh demonstrated the utility of directly injecting cyanoacrylate into AVMs and aneurysms in dogs. Encouraged by these results, Kerber performed the first endovascular embolization of an inoperable intracranial AVM using isobutyl-2-cyanoacrylate (IBCA) and his calibrated-leak balloon catheter in 1974.

One of the technical problems with IBCA was the rapid rate at which it polymerized, sometimes causing adhesion of the catheter to the wall of the artery. When this occurred, the catheter had to be left in place. To address this issue, n-butyl-cyanoacrylate (NBCA) was developed. By varying the concentration of the NBCA in the glue mixture, the polymerization rate could be adjusted according to the characteristics of the vascular lesion.

A non-adhesive liquid embolic system called Onyx was introduced by Micro Therapeutics, Inc. (Irvine, CA, USA) in 1990. Onyx consists of an ethylene-vinyl alcohol copolymer (EVOH), an acetate with industrial applications, suspended in a black tantalum powder that provides contrast under fluoroscopy and is dissolved in dimethyl sulfoxide (DMSO), an organic solvent. Three formulations are available, which vary by the percentage of EVOH in the mixture, providing different viscosities. Two formulations, Onyx-18 and Onyx-34, are intended for use in AVMs. The third, called Onyx HD-500, consists of 20% EVOH and is intended for use in aneurysms. For presurgical embolization of AVMs, Onyx has been received favorably. A limiting factor in its use is the solvent, DMSO, which is angiotoxic. Also, Onyx may only be used with high-pressure catheters that are compatible with DMSO. Ethanol has been used in the past for tumor embolization, but it is extremely toxic to normal tissue, which limits its utility.

Platinum coils may also be used in treating some AVMs and arteriovenous fistulas (AVFs). In particular, so-called fibered coils have been particularly useful in treating high-flow AVFs. Cesare Gianturco at the M.D. Anderson Hospital and Tumor Institute in Texas introduced the fibered coil—a steel coil with a wool tail—in 1975. Fibered coils now usually consist of a platinum core with a coating made of a fibrous material such as Dacron, which creates a rough surface that allows the coil to firmly plant itself at a site of high-flow fistulous communication.

109.4.3 Aneurysms

Many of the endovascular strategies implemented for AVMs were also applied to aneurysms. However, the treatment of aneurysms also has its own unique history of invasive neurosurgical methods that eventually evolved into endovascular approaches. Carotid artery ligation was an early, indirect surgical procedure for treatment of intracranial aneurysms as well as for other types of intracranial pathology and vascular injuries. Norman McCormish Dott of Great Britain is given credit for the first *direct* treatment of an intracranial aneurysm in 1932 in which he used muscle from the patient's thigh to *wrap* the dome of an ICA aneurysm near the origin of the MCA. Subsequent reports on aneurysms treated by wrapping were made by Wilhelm Tönnis, Walter Dandy, and Geoffrey Jefferson.

Aneurysm *trapping* was introduced in 1936 by Walter Dandy. Using this technique, Dandy isolated a cavernous ICA aneurysm by ligating the cervical ICA and clipping the supraclinoid ICA. Dandy made a major contribution in 1937 when he reported his results on clipping a posterior communicating artery aneurysm at its neck and cauterizing the dome. The aneurysm clip underwent many modifications throughout its development over the years, as did the microsurgical approach to aneurysms, most notably those developed by Mahmut Gazi Yasargil at the University of Zurich and John L. Fox at West Virginia University Medical Center.

Direct, endosaccular injection of foreign bodies into aneurysms to induce thrombosis may be considered the most immediate precursor to endovascular embolization. Attempts to induce thrombosis in systemic arteries and aneurysms are discussed in the literature as early as the nineteenth century. Alfred Velpeau in 1831 and Benjamin Philips in 1832 induced intravascular thrombosis by temporarily inserting needles into the lumen of an artery. They suggested that this method might be used for treating aneurysms. Years later, in 1847, Luigi Ciniselli used a method called galvanopuncture to treat thoracic aortic aneurysms. In this method, too, needles were temporarily inserted into the aneurysm, but in addition, a current was passed through the needles to induce thrombosis. In 1863, Charles H. Moore and Charles Murchison attempted to induce thrombus formation in a giant saccular aneurysm of the ascending aorta by inserting a fine iron wire into the aneurysm. The aneurysm grew in size over the ensuing postoperative days, and the patient ultimately died nearly 5 days after the surgery from what the investigators diagnosed on autopsy as pericarditis.

Arthur Blakemore and Barry King pioneered a similar method at Columbia University Medical Center by which they successfully treated an abdominal aortic aneurysm and reported the results in *JAMA* in 1938. Collaborating with Sidney Werner of the Neurological Institute at Columbia, they used this technique to perform the first endosaccular coiling of an *intracranial* aneurysm [9]. Their patient was a 15-year-old girl who presented with progressive vision loss in her right eye. After attempts at carotid ligation were unsuccessful in relieving her symptoms, Werner and his colleagues used a transorbital approach to insert 30 ft. of silver enameled wire directly into the aneurysm (◘ Fig. 109.4). They then heated the wire to induce thrombosis. The operation was technically successful and the aneurysm was stabilized.

Throughout the 1960s, endosaccular treatments were attempted by various neurosurgeons in order to induce aneurysmal thrombosis. These methods included Sean Mullan's electrothermic coagulation (electrothrombosis), Mullan's technique of injecting beryllium copper and copper wire, John P. Gallagher's «pilojection» in which horse or hog hair was injected, and injection of an iron particle suspension with collection of the iron particles in the aneurysm dome by a stereotactically placed magnet, pioneered independently by John Alksne et al. and Hubert L. Rosomoff.

The 1960s also saw the use of the magnetically guided catheter, based upon Frei and colleagues' POD, for superselective catheterization and treatment of intracranial aneurysms. This technology became popular with clinical scientists for several years. Yasargil conceived the idea of using magnetically guided catheters in combination with iron particles to embolize aneurysms and discussed it with Robert Rand at the University of California, Los Angeles. After extensive experimentation, Rand's pupil, John Alksne, ultimately succeeded at implementing this concept in 1968. Subsequently, in 1974, Hilal and colleagues at the Neurological Institute of Columbia University

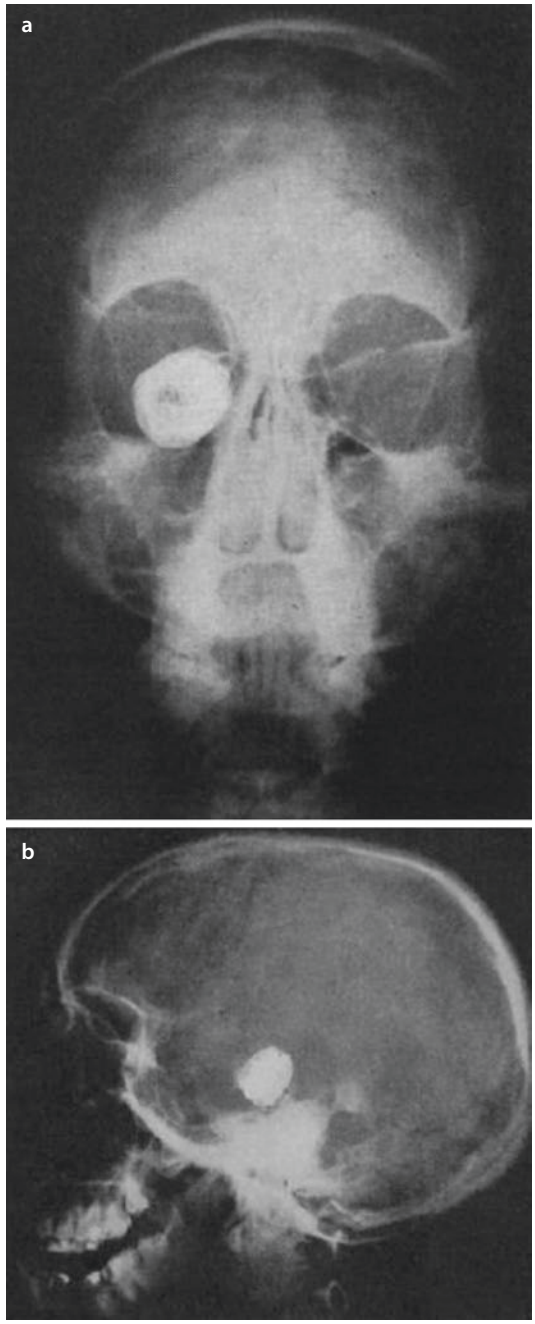

Fig. 109.4 Posteroanterior **a** and lateral **b** radiographs following the first endosaccular coiling of an intracranial aneurysm by Werner et al. [9] in 1941

reported their results on the combined use of electrothermic thrombosis with the magnetically guided catheter to embolize aneurysms, including the partial occlusion of a basilar artery aneurysm.

Use of endovascular balloon techniques began to evolve in the 1960s and the 1970s with the introduction of the Fogarty catheter in 1963. In 1964, similar to what they had done with AVMs, Luessenhop and Velasquez used their glass chamber, surgically attached to the ECA, to catheterize the ICA and advance a silicone balloon-tipped catheter to the neck of a posterior communicating artery aneurysm. Angiograms obtained during and after temporary inflation of the balloon revealed transient isolation of the aneurysm from the rest of the circulation. Although this study did not achieve permanent aneurysm occlusion, it nonetheless left an indelible mark on the history of aneurysm treatment by demonstrating the feasibility of distal selective catheterization and balloon occlusion of an aneurysm by an endovascular approach.

Serbinenko's report on the use of balloon-tipped flow-guided catheters and latex detachable balloons in 1974 was a landmark study, which essentially made endovascular balloon occlusion of intracranial aneurysms a reality for years to come. Extensive clinical experience was gathered by this method in the 1980s and the early 1990s. Through this experience, several problems with endovascular balloon therapy became apparent. One of the issues was that the balloons in use could not always conform to the irregular shape of the aneurysms and therefore could not fully occlude them. This allowed for a water-hammer effect from pulsating blood that promoted aneurysm recanalization and enlargement. Additionally, balloons tended to deflate over time if not filled with a solidifying agent such as HEMA (2-hydroxyethyl methacrylate). As a result, the practice of occluding aneurysms with balloons was eventually abandoned for more sophisticated techniques.

Although the use of coils for arterial occlusion was introduced in 1975 by Gianturco et al., who reported their results in the *American Journal of Roentgenology*, coils were not applied to intracranial aneurysm treatment until 1988 by neuroradiologist Sadek Hilal and neurosurgeon Robert Solomon at Columbia University. In a letter to the *Journal of Neurosurgery* editor in 1992 regarding Italian neurosurgeon Guido Guglielmi's published results on endovascular electrothrombosis, Hilal and Solomon described and illustrated their occlusion of intracranial aneurysms using platinum coils and electrothrombosis. Pushable platinum coils were subsequently introduced in 1990–1991 by Grant Hieshima, Randall

T. Higashida, Van V. Halbach, Christopher F. Dowd, and their colleagues at the University of California in San Francisco. There were several drawbacks to the use of these coils, including poor physical compliance, poor control over delivery of the coils, and inability to retrieve the coils after placement.

The Guglielmi detachable coil (GDC) was developed by neurosurgeon Guido Guglielmi in collaboration with engineer Ivan Sepetka of Target Therapeutics, Inc. Its mechanism and use on the first patients were described in the literature in 1991 [10], beginning a new era in aneurysm treatment. The GDC uses an electrolytic detachment mechanism to release a platinum coil attached to the tip of a stainless steel delivery wire. The electric current that releases the coil is also purported to induce coagulation in the aneurysm by electrothrombosis. The GDC received approval for use in the USA by the Food and Drug Administration (FDA) in 1995.

The main characteristics of the GDC that contribute to its safety and efficacy are its controlled delivery, retrievability, flexibility, and softness of its platinum coils. Bare platinum coils like the GDC remain in use today, but they are limited in their ability to achieve high density in large, wide-necked, or complex aneurysms, increasing the risk of coil compaction and aneurysm recanalization. Coil engineering as well as coiling techniques have developed over the years to address these issues, to minimize aneurysm recurrence rates. Coils have been manufactured with complex three-dimensional shapes, variable degrees of stiffness, various coatings, and different detachment mechanisms. One example is the Matrix detachable coil, which was introduced in the early 2000s by Target Therapeutics, Inc. These platinum coils are coated with a bioactive, bioabsorbable copolymer of polyglycolic and polylactid acid that promotes an inflammatory response that might decrease recurrence rates. Hydrogel-coated coils (HydroCoil, Microvention, Aliso Viejo, CA, USA), which were also introduced in the same time period, are coated with a cross-linked hydrogel that expands 3–9 times the initial coil diameter to more densely pack an aneurysm and minimize coil compaction.

Balloon-assisted coiling or balloon remodeling is a technique that was developed in the late 1990s by Jacque Moret and colleagues for treating wide-necked aneurysms. In this method, a balloon is inflated across the neck of the aneurysm during coil delivery, which stabilizes the microcatheter and forces the coils to conform to the aneurysm shape while preventing them from herniating into the parent vessel.

Stent-assisted coiling is another method that may be used to treat aneurysms for which standard endovascular therapy may be problematic. The idea of intravascular stenting for diseased vessels was introduced by Dotter and Judkins at the University of Oregon in 1964 and demonstrated experimentally by Dotter in 1969. In 1995, neuroradiologists Ajay Wakhloo of the State University of New York at Buffalo and Glen Geremia at Rush-Presbyterian-St. Luke's Medical Center in Chicago published their results on the use of stents in experimentally created carotid aneurysms in dogs, building a foundation for alternative endovascular methods of treating broad-based saccular and fusiform aneurysms. Since then, stents have been designed for use in the intracranial circulation, as opposed to the early, stiffer stents that were manufactured for coronary applications, and are in regular use.

The first stent manufactured specifically for intracranial use was the Neuroform stent (Boston Scientific) designed by Peter Kim Nelson at New York University. Composed of Nitinol, a nickel-titanium alloy, the Neuroform stent is an example of so-called shape memory alloy recoverable technology (SMART). That is, the stent retains the ability to assume a predetermined shape after deployment. Attempts have been made at using such «conventional» intracranial stents as monotherapy for wide-neck aneurysms. By this methodology, a stent is deployed across the neck of the aneurysm in order to remodel the parent vessel-aneurysm complex in such a way that blood flow is diverted away from the aneurysm and through the parent artery. More commonly, however, the role of stents in the treatment of aneurysms has been as an adjunct to coil embolization, functioning in a similar capacity to balloons in balloon-assisted coiling by preventing coils from protruding into the parent artery. New, recently marketed stents such as Silk (Balt Extrusion, France) and Pipeline (Covidien, Mansfield, MA, USA), on the other hand, have been specifically designed as flow diverters. These stents, in principle, could obviate the need for coiling in certain cases, but their clinical efficacy will require further evaluation. Finally, embolization

of aneurysms with liquid embolic agents such as the viscous Onyx HD-500 has been performed but is still a relatively new procedure and under evaluation.

109.4.4 Arterial Stenosis and Revascularization

Revascularization of carotid and intracranial arterial stenoses using angioplasty and stenting was basically an extension of methods developed for peripheral and coronary atherosclerosis. As these topics are eloquently covered in detail elsewhere in this book, what is presented here is a concise overview emphasizing those aspects germane to interventional neuroradiology.

Cardiac surgeon Michael DeBakey is credited with performing the first successful extracranial carotid endarterectomy (CEA) in 1953 at Baylor University College of Medicine. The number of CEAs performed throughout North America and Europe increased dramatically in the 1970s and the 1980s, despite the lack of properly controlled clinical trials and only anecdotal evidence to support its efficacy. Several large-scale clinical trials followed in the 1990s, and CEA soon became the gold standard by which other interventions for treating carotid stenosis are gauged.

In 1964, Dotter and Judkins reported their results on peripheral transluminal dilatation in atherosclerotically diseased lower-extremity vessels using a dilating catheter advanced through the atheroma over a guide catheter in the journal *Circulation* [11]. Andreas Grüntzig subsequently demonstrated the use of an angioplasty balloon catheter to dilate stenotic vessels in 1974. Grüntzig followed up with the first percutaneous transluminal coronary angioplasty (PTCA) in 1977 in a letter to the *Lancet*. Grüntzig presented a more extensive clinical experience on the uses and limitations of PTCA in 1979. Concurrently, metallic stents were designed to augment the effects of angioplasty to treat stenotic bile ducts and arteries. The use of metallic stents to bridge diseased vascular segments was first studied experimentally in dogs by Dotter in 1969 using a spiral stent that was basically a spring. The concept did not progress until the 1980s, however, when a variety of metallic stents were introduced to treat peripheral vascular disease. In the 1990s, stents began being used to treat extracranial carotid stenosis.

Balloon angioplasty for carotid artery disease was introduced in 1980, at which time Kerber performed the first successful angioplasty for carotid stenosis. Studies of its efficacy were performed in the 1980s and the 1990s. By 1995, early results showed very high technical success rates and low morbidity, potentially comparable to those of CEA. Angioplasty began to be recognized as the preferable choice for carotid revascularization in patients with significant co-morbidities. The major complications associated with carotid angioplasty alone, however, were the generation of embolic debris, iatrogenic arterial dissection, and restenosis. To overcome these factors, stenting in conjunction with angioplasty was introduced based on favorable experiences with this combined strategy in coronary artery intervention. The next major technological advancement was the distal embolic protection device. While early studies demonstrated significant reductions in complication rates when distal protection devices were used during stent-angioplasty, even lower rates than those observed with CEA, more recent trials emerged suggesting either modest benefit to stenting or at least non-inferiority compared with CEA.

Reports of using balloon angioplasty to treat *intracranial* atherosclerotic narrowing began to appear in the 1980s [12]. It is important to recognize that the intrinsic properties of the cerebral blood vessels compared to coronary blood vessels, and even atherosclerotically narrowed cerebral arteries compared to non-stenotic cerebral vessels, impose technical limitations on the design of catheters, balloons, and stents for the purpose of safely performing intracranial endovascular revascularization. With the development of microballoon catheters and balloon expandable stents that were capable of being navigated through the small intracranial vessels, more studies on endovascular intracranial revascularization were seen in the 1990s. These studies reported >90% technical success rates and 0–20% complication rates. Intermediate-term clinical benefits were demonstrated by studies in 2004–2005, again with high technical success rates >90% and relatively low peri- or post-procedural stroke or death rates of about 4–7%. Given the poor prognosis of patients with intracranial arterial stenosis >50%, the results of these initial studies were deemed sufficient to formulate the general recommendation that patients who have failed maximal

medical therapy undergo endovascular intervention. Those guidelines may be revised, however, as a result of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, which was prematurely halted on 5 April 2011 due to safety and efficacy concerns. The SAMMPRIS trial, which began in November 2008 with funding from the National Institute for Neurological Disorders and Stroke (NINDS), is the first randomized multicenter trial to compare medical management alone versus aggressive medical management plus angioplasty and stenting in patients with symptomatic high-grade (70–99%) stenosis of a major intracranial artery. The study's Data Safety Monitoring Board halted enrollment in the study after a review of the accumulated data demonstrated that 14% of patients treated with angioplasty and stenting experienced a stroke or died within the first 30 days after enrollment compared with 5.8% of patients treated with medical therapy alone. The trial data currently available indicate that aggressive medical management alone is superior to angioplasty plus stenting in patients with recent symptoms and high-grade intracranial arterial stenosis.

109.4.5 Acute Ischemic Stroke

Ischemic stroke is a major cause of disability and death in the developed world. Endovascular therapeutic options for acute stroke include pharmacologic thrombolysis and mechanical revascularization. Although intra-arterial thrombolysis using plasmin was first demonstrated successfully in 1958 by Bernard Sussman and Thomas Fitch on an acutely occluded ICA, subsequent clinical trials did not convincingly demonstrate the benefit of pharmacological intervention for many years. In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) study demonstrated the effectiveness of early thrombolysis with intravenous (IV) recombinant tissue plasminogen activator (rt-PA). One of the main limitations to IV thrombolysis is the 3-h time window from symptom onset within which current guidelines require it be administered.

Intra-arterial injection of thrombolytic agents was a logical progression from the IV method, offering theoretical advantages of more quickly administering rt-PA in a relatively high local concentration directly at the site of occlusion. The Prolyse in Acute Cerebral Thromboembolism II (PROACT II) study, published in 1999, clearly demonstrated the safety and efficacy of intra-arterial rt-PA when delivered within 6 h of symptom onset.

Several devices were used off-label for attempted mechanical thrombectomy with the introduction of endovascular foreign-body retrieval devices in the 1980s, but the first mechanical thrombectomy devices specifically for acute stroke became available in the 1990s. Of the seven devices that were actually evaluated in trials for acute stroke intervention, two have received FDA approval: the Merci Retriever (Concentric Medical, Mountain View, CA, USA) in 2004 and, more recently, the Penumbra System (Penumbra, Inc., Alameda, CA, USA). The Merci Retriever, which was evaluated in the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, is a corkscrew-like device that is advanced into the occlusive thromboembolus and used to pull the clot back into the guide catheter. The Penumbra System, which was evaluated in the Penumbra Pivotal Stroke Trial, uses aspiration to extract the clot, while a stent-like wire device is used to mechanically disrupt it. These trials have established a therapeutic window for mechanical thrombectomy of 8 h following symptom onset in patients who are not candidates for or are failing IV thrombolysis. Angioplasty, occasionally with stenting, is another commonly used mechanical method for acute stroke revascularization. This strategy is an off-label use of currently available intracranial stents, as no stent currently exists specifically for acute stroke therapy. The next generation of stroke devices called stent retrievers use stent-like devices to withdraw the occlusive thromboembolus, and are undergoing testing now.

109.5 Conclusion

This chapter is an historical snapshot of a rapidly developing field. In discussing the innovations, developments, and tools that enabled the endovascular treatment of cerebral aneurysms, arteriovenous malformations, atherosclerotic disease, and stroke, we have described the basic tools and techniques that have also been used to treat many other diseases of the head, neck, and spine. In addition to the applications

already mentioned in this chapter, interventional neuroradiology now plays a central role in the medical management of various other scenarios, including dural arteriovenous fistulas, cavernous carotid fistulas, presurgical embolization of tumors, epistaxis, venous and lymphatic malformations of the face, head, and neck, vasospasm, arterial dissections, vein of Galen malformations, and dural sinus thrombosis.

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