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# A New Liquid Material for Embolization of Arteriovenous Malformations

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We have developed a liquid material for embolization of arteriovenous malformations that is a mixture of ethylene vinyl alcohol copolymer and metrizamide dissolved in dimethyl sulfoxide. Upon contact with blood, dimethyl sulfoxide rapidly diffuses into the blood and forms an ethylene vinyl alcohol copolymer elastic soft sponge that obstructs both the feeder and the nidus. The material, which is not adhesive, was used for embolization of three left cerebral arteriovenous malformations with satisfactory results.

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Some cerebral or dural arteriovenous malformations (AVMs) are difficult or impossible to remove surgically because of their size and location. For these AVMs, embolization is the primary radical or adjunctive treatment and is performed by using cyanoacrylate derivatives such as isobutyl 2-cyanoacrylate (IBCA) [1-4]. However, IBCA can glue the balloon to the artery and sometimes polymerize within the catheter, leading to an incomplete injection. In addition, polymerized cyanoacrylate forms a very hard mass, which is difficult to remove. To overcome these disadvantages, we developed a radiopaque liquid material for embolization. The material was clinically applied in three cases of AVM.

## Materials and Methods

The embolizing liquid we developed is a mixture of 5 g of solid ethylene vinyl alcohol copolymer (EVAL) and 35 g of powder metrizamide dissolved in 60 g of dimethyl sulfoxide (DMSO) as a solvent at room temperature (Table 1). After the EVAL and metrizamide were completely dissolved in DMSO, the mixture was sterilized at 121° for 20 min. EVAL, a medically graded copolymer, consisted of 0.67 mol fraction polyethylene, and 0.33 mol fraction polyvinyl alcohol. DMSO was selected as the solvents for EVAL because it readily diffuses in water and reduces intracranial pressure [5-8]. In an *in vitro* experiment, EVAL was injected into water through an 18-gauge needle. In about 3 sec, a white gellike droplet had formed; it had a sponglike consistency within 15 sec. In dogs, injection of the embolic agent into a renal artery occluded vessels as small as 80  $\mu$ m in diameter, and histologic examination revealed no inflammatory reactions. There were no histologic changes in the endothelial cells or the smooth muscle cells that were directly in contact with EVAL. Since the sponge is elastic and soft, during surgery it is easy to cut and handle the nidus packed with an EVAL sponge. For the injection of EVAL, percutaneous transfemoral catheterization was performed. The introducing catheter was guided into the internal carotid artery or the vertebral artery. Through this introducing catheter, a calibrated leak balloon catheter was introduced and positioned within the feeding artery. First, the contrast material was injected superselectively. By angiography, we ascertained whether the catheter tip was guided distally enough to the proper feeder so as not to involve the normal branches. After the injection of the contrast material, an amyntal test was performed by injecting 1 ml of thiopental sodium (50 mg/ml) through the microcatheter into the feeding pedicle. Since it was possible that small normal branches distal to the tip of the microcatheter were not visualized by angiography, immediately after the injection, the neurologic status was determined by whether or not the thiopental

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**TABLE 1: Composition of the New Liquid for Embolization**

Material	Amount (grams)
Dimethyl sulfoxide	60
Ethylene vinyl alcohol copolymer	5
Metrizamide	35
Total dose	100

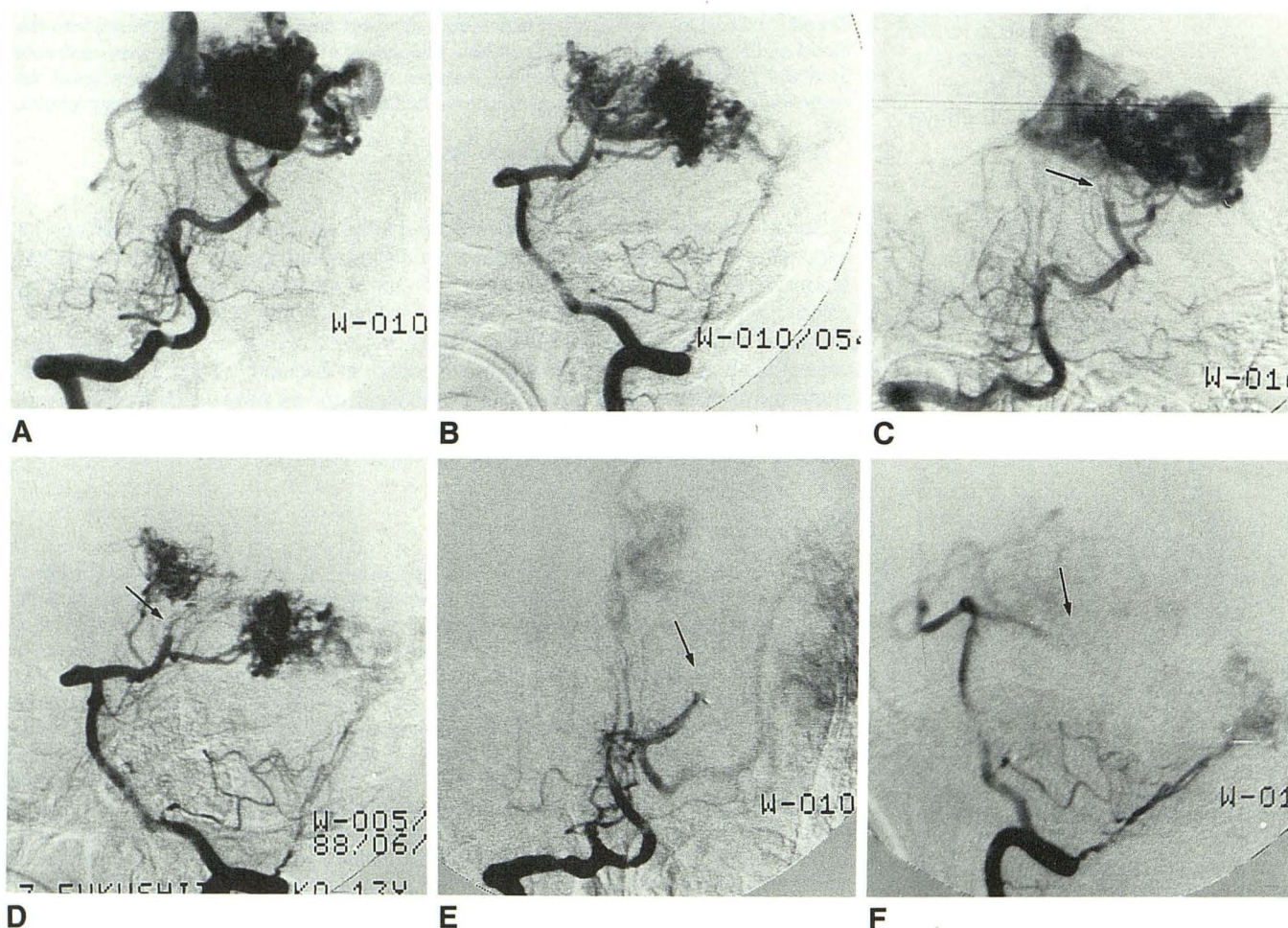
sodium elicited a neurologic deficit. After confirming no neurologic deficit, 2 ml of DMSO were injected to irrigate the catheter lumen, and this was followed by injection of the EVAL mixture under fluoroscopic control. The injection was continued and repeated until the feeding pedicle and the nidus were completely occluded. Since the material is not adhesive, multiple injections could be performed. Usually, 0.4 to 0.5 ml of the embolic agent was sufficient to occlude a single pedicle and its perfusion territory. As many feeders as possible were catheterized and embolized. After embolization, the

catheter was withdrawn and the puncture site was compressed until hemostasis was complete.

## Case Reports

### Case 1

A 13-year-old girl noticed a gradual onset of right exophthalmos 2 years before admission and consulted an ophthalmologist, who noted right homonymous hemianopia. At that time, cerebral angiography revealed a large left temporooccipital AVM, which was deemed unresectable. One year before admission, the patient suffered transient right hemiparesis and began to perform poorly at school. Two months before admission, she suffered from frequent generalized convulsions that finally progressed to status epilepticus. After recovering from the status epilepticus, she was tetraparetic, and completely aphasic, probably the result of prolonged global ischemia. She was referred to our hospital. Cerebral angiography showed a large temporooccipital AVM that was fed by branches of the left posterior



**Fig. 1.—Case 1.**

A and B, Preoperative vertebral angiograms, anteroposterior (A) and lateral (B) views. Large temporooccipital AVM is fed by temporal branches of middle cerebral artery and posterior cerebral artery.

C and D, Anteroposterior (C) and lateral (D) views. The part of nidus fed by parietooccipital artery was embolized (arrow in C and D).

E and F, Anteroposterior (E) and lateral (F) views after embolization of calcarine and lateral posterior choroidal artery. Since the three main branches of the posterior cerebral artery were embolized, the main trunk of that artery was opacified to the branching point (arrow in E and F).

(Fig. 1 is continued on the opposite page.)



cerebral and left middle cerebral arteries (Fig. 1). The AVM drained via the left Trolard's vein, Galen's vein, transverse sinus, right petrosal sinus, and right superior ophthalmic vein. The right exophthalmos was due to the reverse flow through the right superior ophthalmic vein.

Embolization was performed in two stages. At first, three feeders from the left posterior cerebral artery were catheterized. In each feeding artery, thiopental sodium was injected. After confirming that there was no neurologic deficit, 0.3 to 0.5 ml of EVAL was injected. After this procedure, the part of the AVM that was fed by the posterior cerebral artery was occluded. At the second stage, the AVM fed by the left middle cerebral artery was embolized. The same procedure was repeated to embolize the middle and posterior temporal arteries. After the second stage of embolization, the nidus was almost entirely embolized. The patient was kept under strict blood pressure control for 24 hr after embolization. Follow-up angiography, performed 2 weeks after the procedure, confirmed that more than 95% of the nidus was occluded. Subsequently, the tetraparesis and aphasia gradually improved.

#### Case 2

A 53-year-old woman had been healthy until 1 year prior to admission, when she began to suffer from severe headaches. There were no neurologic deficits. CT revealed an intracerebral hemorrhage. Cerebral angiography showed an AVM fed by the left posterior temporal artery. The AVM was also opacified through the fetal type of posterior communicating artery, as evidenced by a left internal carotid angiogram (Fig. 2). A microballoon catheter was introduced through the right femoral artery. Since the left vertebral artery was tortuous and narrow, the balloon was advanced to two feeding pedicles via the left internal carotid and posterior communicating arteries. The feeding pedicles were the posterior and middle temporal arteries of the posterior cerebral artery. After an amytal test in each pedicle, 0.5 ml and 1.0 ml of EVAL mixture were injected into these two feeding pedicles, respectively. Ninety-five percent of the AVM was occluded. The patient was kept under strict blood pressure control for 24 hr after embolization. Angiography 2 weeks after embolization showed only a small residual AVM that was fed by the

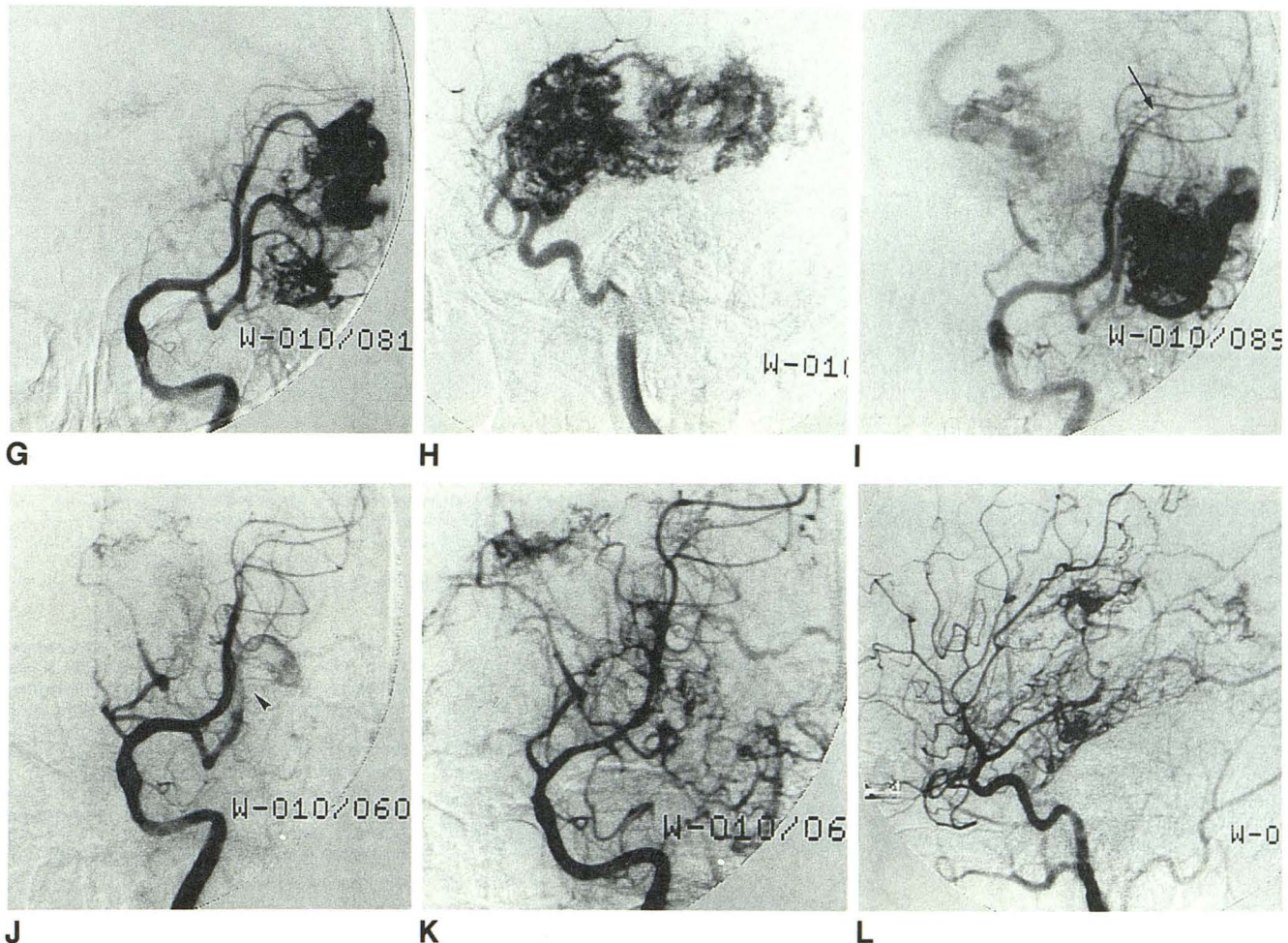


Fig. 1—(Continued).

G and H, Preoperative left internal carotid angiograms, anteroposterior (G) and lateral (H) views. Large temporooccipital AVM is fed by temporal branches of middle cerebral artery.

I, The part of AVM fed by posterior temporal artery was embolized (arrow).

J, Angiogram done after embolization was complete (arrow).

K and L, Follow-up angiography, anteroposterior (K) and lateral (L) views, 2 weeks after embolization. The small part of nidus fed by medial posterior choroidal artery and the tiny temporal branches were still opacified. Almost the entire nidus was occluded.



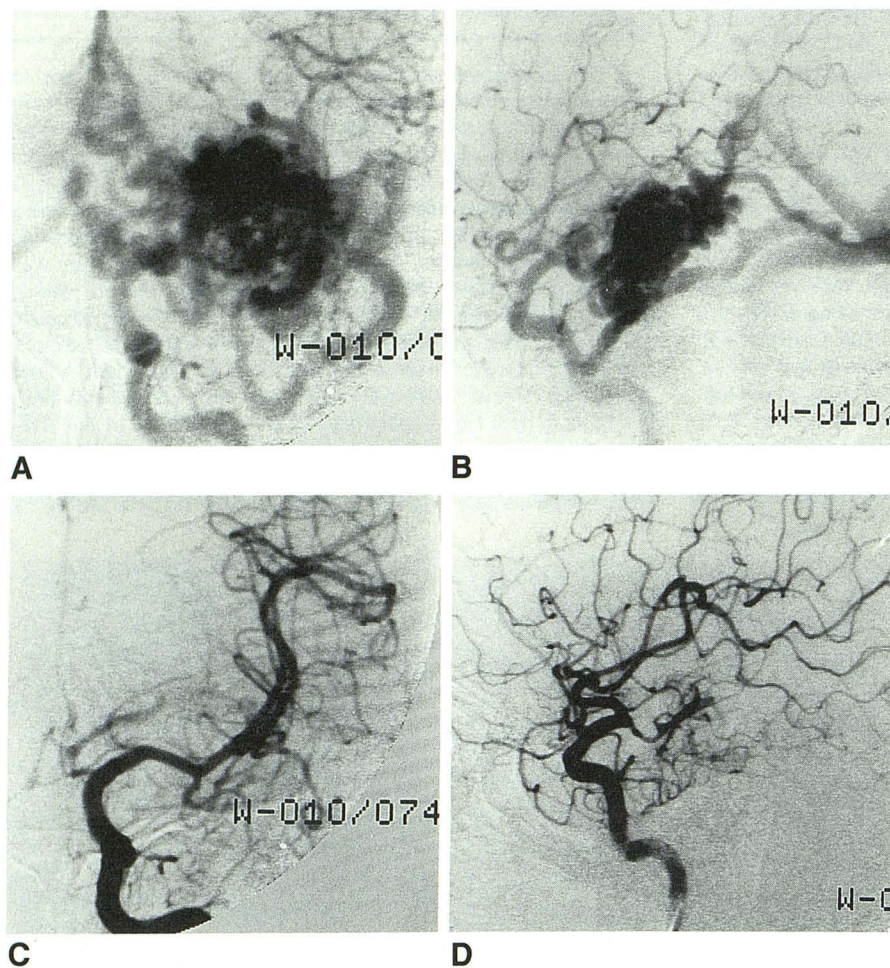


Fig. 2.—Case 2.

A and B, Left internal carotid arteriograms, anteroposterior (A) and lateral (B) views. The large AVM at medial temporal lobe was opacified. The feeders were the posterior and middle temporal arteries of the left posterior cerebral artery.

C and D, After embolization, almost the entire nidus was occluded.

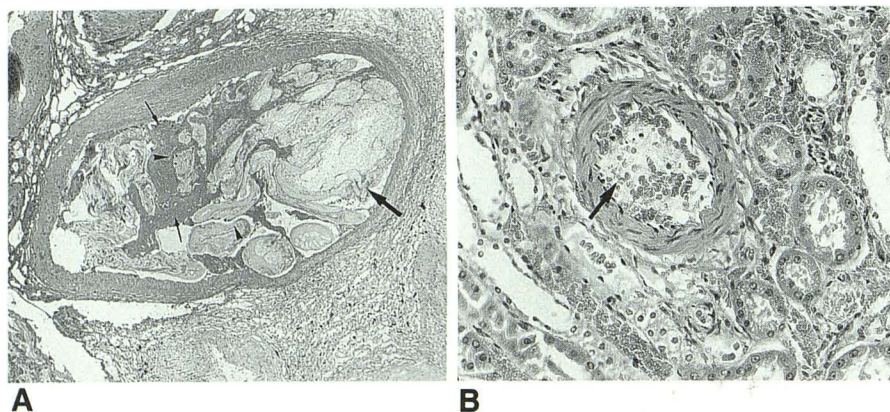


Fig. 3.—A, Photomicrograph of EVAL-embolized AVM from case 2. EVAL sponge is indicated by large arrow. There were no inflammatory infiltrates in vessel wall; there were partly organized thrombi among the EVAL sponges (small arrows); and a small number of giant cells were observed (arrowheads). (H and E,  $\times 40$ )

B, Photomicrograph of EVAL-embolized renal artery (arrow). The arteries with a minimum size of 80  $\mu$ m were occluded with EVAL. There were no inflammatory infiltrates. (H and E  $\times 100$ )

anterior temporal branch of the middle cerebral artery. There were no neurologic symptoms, but a neurologic examination revealed only right homonymous upper quadrantic anopsia, presumably as a consequence of excessive injections into the feeding artery that branched directly from the posterior cerebral artery. This AVM was completely

resected during left temporal craniotomy 25 days after embolization. The histologic study showed no inflammatory reaction in the vessel wall in contact with the EVAL. There were partially organized thrombi scattered among the EVAL sponges and a small number of giant cells near the EVAL fragments (Fig. 3). Bleeding from the nidus was



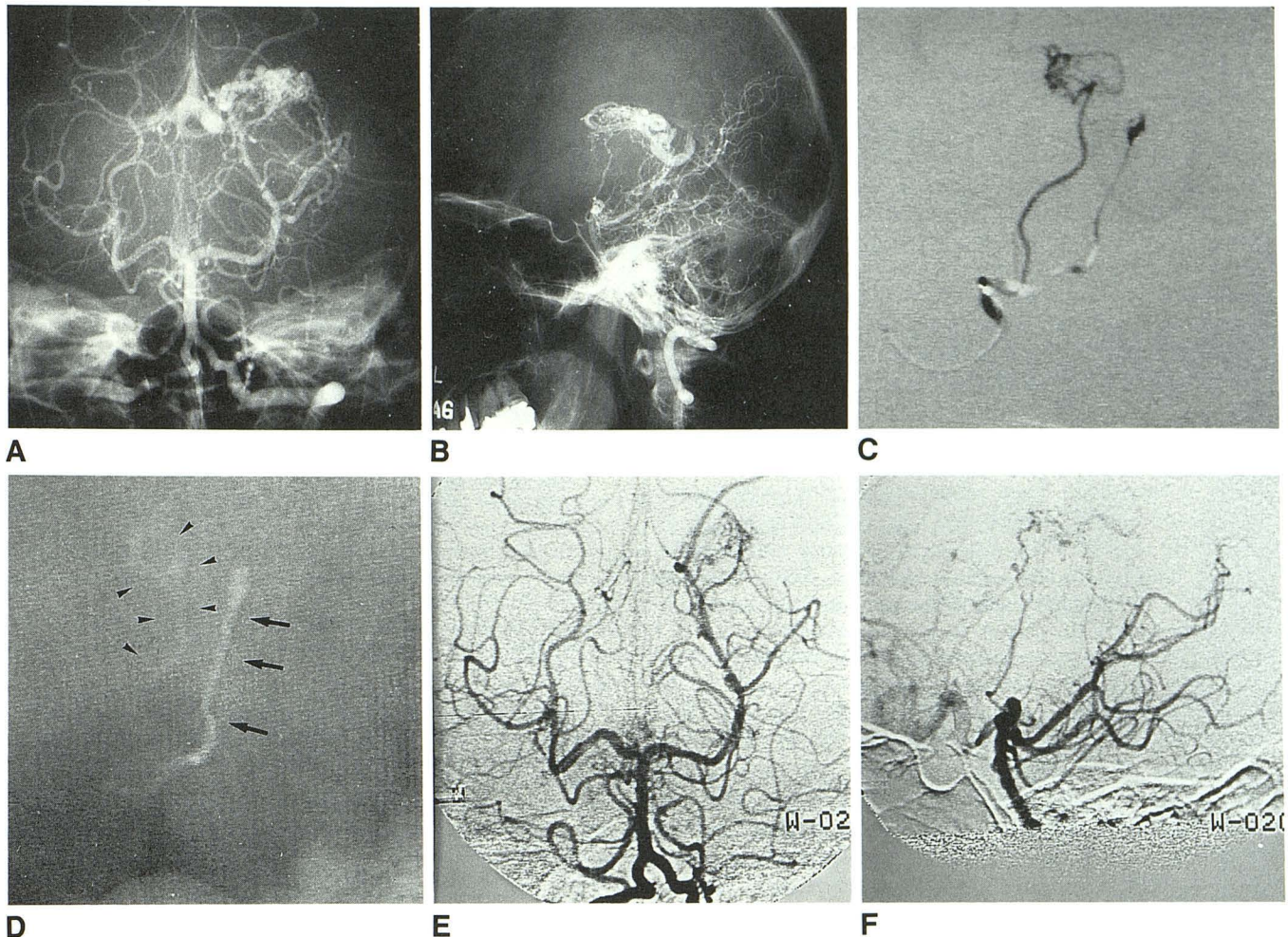


Fig. 4.—Case 3.

A and B, Left vertebral angiograms show a thalamic AVM fed by left thalamoperforating arteries and lateral posterior choroidal artery.

C, Leak balloon was guided to the left lateral posterior choroidal artery.

D, New embolizing liquid was injected. New material was radiopaque and instantly occluded the nidus (arrows and arrowheads). Since metrizamide mixed in the EVAL and DMSO diffuses quickly into the blood, part of the EVAL in the nidus was not well opacified (arrowheads). Usually, diffusion of metrizamide was complete within 5 min.

E and F, Postembolization angiograms show that about three quarters of nidus was occluded.

minimum and the EVAL was soft and easy to remove. Postoperative angiography showed complete disappearance of the AVM. The patient returned to her previous work with no problems.

#### Case 3

A 26-year-old woman had been healthy until the onset of severe headaches. She was somnolent upon admission. There were no focal neurologic deficits. CT demonstrated intraventricular hemorrhage and a vascular malformation in the left paraventricular region. Cerebral angiography revealed an AVM fed by the left thalamoperforating arteries and left lateral posterior choroidal artery (Fig. 4). Prior to surgery, percutaneous transfemoral embolization was performed. With monitoring digital subtraction angiography, the microballoon catheter was advanced into the left lateral posterior choroidal artery, and 0.2 ml of the new embolizing liquid was injected after an amytal test. The embolizing liquid, clearly visible by fluoroscopy, filled the large

part of the nidus. The balloon was deflated and the catheter was withdrawn without any difficulty. Postembolization angiography demonstrated that about 75% of the nidus was occluded. After embolization, right upper quadrantic anopsia developed, probably as a result of interference of the blood supply to the part of the lateral geniculate body. There was no other neurologic deficit.

#### Discussion

EVAL is a copolymer of polyethylene and polyvinyl alcohol. Polyethylene has been used in artificial joints for implantation [9] and PVA has frequently been used as particulate material for artificial embolization [10]. Both are biocompatible polymers that have been used in implantation. In addition, histologic examination of AVMs embolized with EVAL showed no associated inflammatory reaction. Polyethylene is a hydropho-



bic polymer and PVA is a hydrophilic polymer, so the copolymer EVAL has both hydrophobic and hydrophilic properties. DMSO was chosen as a solvent of EVAL because it has been used in humans and its physiologic properties have been well documented [5-8]. Up to a 20-40% solution was used for IV infusion and as much as 8 g/kg/day was used without evidence of hemolysis or coagulopathy. Hyperkalemia was the only problem, and this was controllable when the maximum dose was given [7]. This amount is much larger than that used for embolization, which requires only 4-5 g in one procedure. To prevent the possibility of EVAL solidifying and occluding the catheter lumen during its injection, we irrigated the catheter with 2 ml of DMSO before injecting the EVAL.

The EVAL and DMSO mixture was of low viscosity and could be easily injected through the narrow lumen of the microballoon catheter, which was 150 cm in length. Since the mixture was not adhesive, it did not obstruct the leak hole at the tip of the balloon. Thus, repeated injections under fluoroscopic control were possible, and this enabled the delivery of a sufficient volume of the mixture to the nidus and pedicles without passage to the venous drainage. Such repeated injection is not possible with IBCA because it instantly occludes the leak hole.

Although the EVAL mixture is useful for embolization, it might not be suitable for some lesions such as a single arteriovenous fistula or an AVM that contains a large arteriovenous fistula, since it is possible that EVAL may pass through the nidus to the venous drainage. The nonadhesive character of the EVAL and DMSO mixture allowed the safe removal of the microballoon catheter. As for recanalization of the embolized AVM, EVAL is not biodegradable and appears to be comparable to IBCA, which is far superior to the particulate embolization. Although almost the entire nidus can be occluded by EVAL, the residual nidus may gradually en-

large. Surgical resection after embolization is necessary when early venous drainage is still observed by postoperative angiography.

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