CEREBRAL ANGIOGRAPHY: A TECHNIQUE USING DILUTE DIODRAS

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The introduction of radio-opaque materials into the fluid-filled cavities of the body has accompanied the development of radiology since its early days. Injection of the vascular system is desirable as a diagnostic measure since blood vessels reach all organs and form there a regular pattern. However, there are two serious disadvantages. First, no material may be injected which can serve as an embolus or which is irritating to the vessels themselves; second, the rapid movement of blood makes the timing of X-rays difficult. Numerous variations in contrast media and techniques have been suggested to meet these difficulties in angiography of different structures.

The brain is especially well suited to study by angiography. It is invested with a system of quite large vessels, displacement of which can be recognized without difficulty; the vessels themselves may be affected by disease; and arteries carrying the entire blood supply are easily reached in the neck. The value of cerebral angiography in diagnosis has been well shown in the work of Moniz,17,18 Elvidge,5 Gross,9 List,14 and many others. Yet the rather tedious procedures requiring special X-ray equipment, the lack of an entirely satisfactory contrast medium, and the possible danger to patients have barred the method from general acceptance. These subjects: contrast media for angiography, and the technique of cerebral angiography, will be reviewed and a method which has been safe and satisfactory in our hands will be presented.

CONTRAST MEDIA FOR ANGIOGRAPHY

The choice among contrast media has been a difficult one, for each material has had certain definite faults. Moniz first used strontium bromide and then sodium iodide, both of which caused serious reactions. In 1931 he adopted thorotrast, a material which produced X-ray films of excellent diagnostic quality and caused little or no immediate reaction. Its drawback lay in its high and lasting radioactivity, together with almost quantitative storage in the reticuloendothelial system.29 Despite this it has been chosen for almost all cerebral angiograms and is looked upon favorably by most of those who have published reports of their work in this field.5,13,18

"Thorotrast" is the trade name for a colloidal preparation of thorium

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dioxide. When studied by the Council on Pharmacy and Chemistry of the American Medical Association in 1932, it was rejected for intravenous injection because of its radioactivity. The thorium which causes this is an unstable element having a pattern of decomposition like that of uranium. It produces a series of daughter elements, each existing in equilibrium with the ones above and below in the series of decomposition, so that the radioactivity remains approximately unchanged. Three emanations are produced by this decomposition, alpha particles or rays, beta rays, and gamma rays. Radium therapy of tumors is accomplished largely by the effect of the beta rays. In toxicity for normal tissues, however, the alpha rays are much the strongest, in ratio with beta and gamma rays as 10,000 is to 100 and to 1. Since their penetration is weak, the alpha rays are easily filtered out when radium is used for therapy. Alpha rays form the predominant emanation of thorium and thus a high toxicity is to be expected.

Two general types of tissue damage have been shown to be caused by the radioactivity of thorium: necrosis which is followed by scarring, and sarcogenesis. Both of these reactions were first observed in watch workers who painted luminous dials. Careful studies of these patients were made by Martland and the insidious nature of the thorium poisoning was brought to light. In experimental animals thorotrast injected intravenously is deposited in the liver, spleen, bone marrow and lymph nodes, and the changes of irradiation damage develop slowly over a period of several years. Sarcoma of the peritoneum was produced in rats by Roussy, Oberling and Guérin with intraperitoneal injections of thorotrast. Selbie was able to cause peritoneal sarcoma with as little as 0.6 cc. of thorotrast.

The ultimate danger of sarcoma in man has been stressed by those who have conducted studies in animals. This complication has failed to appear among patients, however, and those who prefer to use thorotrast have allowed this to outweigh the experimental evidence. The recent case of Mac-Mahon, Murphy and Bates, one of the first patients studied a number of years after thorotrast injection, shows that man is no exception. This patient died at the age of 70 of hemorrhage from a primary endothelial-cell sarcoma of the liver. Seventy-five cc. of thorotrast had been injected 12 years earlier to outline a gumma of the liver. There was widespread irradiation injury, especially in the liver and the hematopoietic system. The greatest concentration of thorotrast lay in the liver and the tumor had originated “in immediate association with the largest single deposition of this material in the body.” The other changes of irradiation are well shown in this case. The liver parenchyma was damaged and extensive fibrosis had occurred in the portal areas. Thorotrast was present in the reticuloendothelial system of bone marrow, spleen, liver and lymph nodes, and all of these structures showed damage. The smooth muscle and elastica of blood vessels were affected.

Findings similar to these were reported earlier by Jacobson and Rosenbaum in a patient who had received thorotrast 5 years before death. Their
patient had not developed sarcoma. Immediate damage to the brain following angiography with thorotrast has been reported by Nordman, by Northfield and Russell, and by Ekström and Lindgren. The lesions were usually microscopic and closely associated with the smaller blood vessels. Small emboli of thorotrast could be seen in the lumens of some of the sectioned vessels. Except in a few cases the injury was not sufficient to have changed the patients' condition greatly.

No quantitative estimation of the power of thorotrast to produce sarcoma in man is possible at present. Probably some injury is caused in most patients who survive 5 to 10 years or more and this danger is ample reason to avoid the use of thorotrast for intravascular injection except in special cases.

In 1939 Gross, Torkildsen, and Pool independently employed diodrast for cerebral angiography. This material, called perabrodil in the European literature, is the 3,5 diodo-4-pyridone-N-acetate of diethanolamine. It contains about 50 per cent fixed iodine, is highly soluble and is stable in aqueous solution. It is excreted quickly and unchanged in the urine following intravenous or subcutaneous injection and is widely used for intravenous urography. Individuals may develop sensitivity to diodrast and for this reason a preliminary ocular or intradermal sensitivity test should be made. No significant systemic responses to diodrast are observed except those attributable to the injection of hypertonic solutions. Thirty-five per cent solutions of diodrast are approximately twice isotonic.

Investigations using experimental animals for cerebral angiography with diodrast have been reported by Gross in 1939 and by Kristiansen and Cammermeyer in 1942. Gross made common carotid injections in dogs under nembutal anesthesia. Five received 30 cc. of a 70 per cent solution, and one each 30 cc. of a 50 per cent solution and a 35 per cent solution. There were no physiological changes observed and no changes in the brain were found when the animals were sacrificed. The angiograms of the first group showed good contrast but those of the animals receiving 35 per cent and 50 per cent diodrast were not of satisfactory diagnostic quality. Kristiansen and Cammermeyer reported 17 injections of 35 per cent perabrodil into the common carotid artery in 13 rabbits without lasting physiological changes. The animals were sacrificed after varying periods and no lesions in the brain were found.

The first group of patients in whom diodrast angiography was reported by Gross received injections of 15 cc. of 70 per cent diodrast. Of the 10 patients studied, 3 had mild Jacksonian convulsions and another, apparently suffering from a neoplasm, developed a hemiparesis 3 days following the angiography. In a later group of 10 patients 50 per cent diodrast was used with good diagnostic results. Only one of these had a mild Jacksonian convulsion.

Torkildsen is reported to have used 35 per cent perabrodil for cerebral arteriograms in 12 patients in 1939. Injections of 18 to 20 cc. were made into the internal carotid artery. There were no complications and the arterio-
grams were of good diagnostic quality. Pool and Alexander used 15 cc. injections of 35 per cent diodrast for angiography in 9 patients without noting undesirable reactions. The visualization was not uniformly satisfactory, however, and no positive findings were reported.

In the lower concentrations (35–50 per cent) diodrast is slightly less dense than thorotrast but it has the great theoretical advantage that the total amount injected may be much greater. Separate injections may be made for stereoscopic arteriograms and for venograms, and two or more of the great arteries supplying the brain may be injected at successive settings. By injecting repeated small doses of the 35 per cent solution satisfactory visualization has been obtained without the occurrence of untoward symptoms.

TECHNIQUE OF ANGIOGRAPHY

Most of the reported carotid injections have been made by surgical exposure of the common or internal carotid artery. A. B. 9. 10. 13. 18 Closed injections of thorotrast have been made by Freeman 9 and by Poppen. 21 Local anesthesia has usually been employed. The apparatus most commonly used consists of a large needle which may be curved, a rubber connecting tube, and a syringe of from 10 to 30 cc. capacity. Vertebral angiograms have been made by direct exposure of the artery in the neck or by retrograde injection of the subclavian artery or carotid artery.

The X-rays are usually made in either of two ways. The best definition is secured by the use of the Potter-Bucky diaphragm. A rapid cassette changer of the type used by Moniz is of value when thorotrast is used since the number of injections must be limited. The ideal solution to this problem would seem to lie in cinematography of the organ to be visualized during the passage of the contrast medium through its vascular network. This has been achieved by Holm 20 who found that new disadvantages appeared. Photographing a fluorescent screen with the best optical system available, he was unable to show detail in the cerebral angiogram approaching that recorded by an ordinary X-ray film. In cases where the general pattern of flow was of greatest interest he favored the use of this method, advising against it when exact detail was important.

CLINICAL OBSERVATIONS

Twenty-five patients ranging in age from 1 year and 10 months to 68 years have received two or more injections of 10 cc. of 35 per cent diodrast during the past 3 years. Light pentothal anesthesia was used for all except 4 young children who received ether. For carotid angiograms the common carotid artery was exposed in the neck; for vertebral injections the artery was exposed just below its entrance into the foramen of the 6th cervical vertebra. Stereoscopic X-rays were made in all cases.

Equipment. The instruments used for angiography, except those needed to expose the artery, are shown in Fig. 1. The only unusual one is the special angiogram needle (Fig. 2) which greatly simplifies the critical stage of injection. It is a number 18 needle having a curve of about 60 degrees with its bevel on the outer side of the curve. A rounded shoulder 4 mm. above the opening is placed eccentrically so that its plane of contact with the artery when the
The instruments used for cerebral angiography.

Fig. 1. The instruments used for cerebral angiography.

A syringe of the type required for angiography may be a dangerous lever against the artery when connected in the usual way. This has been avoided in the past by the use of a rubber connecting tube between the syringe and needle. Such a system is not desirable however since the apparatus becomes unwieldy and the hydraulic system is enlarged, increasing the danger of clotting in the tubing and making the timing of injections more difficult. We have obviated the need for a connecting tube by attaching the syringe to the side of an ordinary three-way stopcock (Fig. 4). The needle is easily held in position and changing of syringes is facilitated. Ten cc. Yale B-D Lok syringes, having metal handles, are used. It is possible to make the injection under much greater control with this type of syringe than with larger ones.

Fig. 2. Angiogram needle.
X-ray Technique. The angiograms were made with the equipment ordinarily used for X-rays of the skull at the Peter Bent Brigham Hospital and at The Children's Hospital. Exposure times of from 0.2 to 0.4 sec. were allowed with the output of the X-ray tube adjusted to provide skull films of normal density with the Potter-Bucky diaphragm.

Operative Procedure. The common carotid artery is exposed through a short transverse incision 2 to 3 cm. above the clavicle. A single loop of moist cotton tape is placed around the artery and attached to a hemostat. While gentle traction is made, the angiogram needle is inserted about 2 mm. above the tape with the stopcock in the off position (Fig. 3). After one

![Fig. 3. The angiogram needle inserted into the carotid artery.](image)

of the 10 cc. Yale B-D Lok syringes containing diodrast has been attached to the side arm of the stopcock the anode of the X-ray tube is started in rotation. The stopcock is turned to connect the syringe and needle and a stream of blood entering the syringe demonstrates the patency of the system (Fig. 4). The injection of 10 cc. is made in approximately 2 seconds, and as the 2 cc. mark is crossed the X-ray technician is asked to expose the film. The actual exposure coincides with the completion of the injection. After the roentgenogram is made the valve is turned off and the syringe is disconnected.

This procedure is repeated for the stereoscopic duplicate and for an anteroposterior arteriogram. The needle is left in place until the X-rays are developed. It is then withdrawn and pressure is made against the arterial puncture until bleeding stops. The wound is irrigated with saline and closed with interrupted silk sutures.

Results. In 25 successive angiograms the X-rays were of satisfactory quality for diagnosis in all but 2. There were positive findings in 9 cases, over one-third of all the patients studied. The syndromes which led us to perform angiography could be divided into four general groups: 10 of the patients had previously had spontaneous subarachnoid hemorrhage; 4 were admitted with
unilateral ophthalmoplegia, one with subarachnoid hemorrhage at the same time; 8 of the remaining patients had other signs of an expanding intracranial lesion, and 4 had multiple hemangiomata. The positive findings of arteriography were as follows: aneurysm of internal carotid artery, 4; aneurysm of middle cerebral artery, 2; arteriovenous angioma, 2; glioma involving the falx, 1.

In no case could untoward symptoms be attributed to the procedure. Two of the patients complained of headache on awakening but the headache disappeared within 24 hours. There was no postoperative fever that could be considered significant in patients who had been anesthetized. Most of the patients complained of some discomfort in the neck on awakening. There were no convulsions or disturbances of motor function. The sutures were removed on the second postoperative day and in all cases the wounds healed well without signs of irritation by the diodrast.

It is worthy of note that 8 of the patients in this group were children, 3 of whom were under 4 years of age. Fig. 5 shows the normal carotid arteriogram in a child of 2 years 3 months. This seems to be a safe method of study of intracranial disease in young patients.

It has been possible to study the brains of two of the adult patients who died a considerable time following angiography. One was a 29-year-old woman with a large glioma of the left parietal lobe involving the falx. An autopsy conducted at the time of death 4 months after the angiogram showed
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no lesion of the brain that could have been caused by the diodrast injection. The second patient was a 23-year-old veteran in whom an aneurysm of the middle cerebral artery had been demonstrated. Two weeks after ligation of the internal carotid artery and 5 weeks after angiography, a fatal subarach-

![Image](Fig. 5. Normal carotid arteriogram; child aged 2 years and 3 months.)

noid hemorrhage occurred. Study of the brain again failed to show histologic changes that could be attributed to the angiography.

The following case histories show the special value of angiography under different conditions.

Case 1. An 8-year-old school boy, previously healthy, entered the hospital on May 28, 1946, in semi-coma. Two days before admission, after taking a cold bath, he complained of a headache and lay down on a couch. Thirty minutes later he could not be aroused. He was taken to another hospital where he was found to be in vascular shock with bloody spinal fluid and right hemiparesis. On admission to The Children's Hospital he was irritable and disoriented. He complained of headache and lay in a position of opisthotonus. The blood pressure was 170/115, there was a right hemiparesis, and the spinal fluid contained 45,000 erythrocytes. An electroencephalogram showed marked slowing over the entire left hemisphere. The patient improved slowly and on June 25 a left common carotid arteriogram demonstrated an irregular collection of dye near the sella turcica, considered to be an aneurysm partly filled by
a blood clot. The carotid artery was ligated on July 11, 1946. The patient was well and active in March of 1947.

Comment. This case shows the possibility of spontaneous subarachnoid hemorrhage, apparently from an aneurysm of the circle of Willis, in childhood. By angiography it was possible to find the source of bleeding and to decide what plan of management should be followed.

Case 2. A 25-year-old housewife entered the hospital on May 20, 1946, in coma of 2 hours' duration. At about 10 a.m., following a normal breakfast, speech became difficult and the patient felt giddy and nauseated. She summoned a friend from a nearby apartment by telephone but by the time the neighbor arrived she could only say, "I don't know." She rapidly grew drowsy and began to vomit projectilely. When she reached the Peter Bent Brigham Hospital the patient was semi-comatose. Both pupils were dilated but reacted to light. The neck was held in opisthotonus. The abdominal reflexes could not be obtained and the right tendon reflexes were hyperactive with positive Babinski and sustained ankle clonus. There were 8100 erythrocytes per c. mm. in the spinal fluid. The general condition improved greatly during the night; the following morning she was sufficiently responsive for right homonymous hemianopsia to be detected. On the 3rd day she was lucid, and aphasia, astereognosis, loss of position sense on the right and diminished sensation to pain on the right were observed. Im-

Fig. 6. Case 2. Arteriovenous aneurysm of posterior parietal artery. (A) Artery. (An) Aneurysm. (V) Vein. (S) Longitudinal sinus.
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Improvement was then rapid; by the 15th day only slight aphasia and right-sided weakness remained. An electroencephalogram showed normal frequencies with amplitude asymmetry suggesting suppressed activity in the occipital region. A left carotid angiogram was made on August 31 revealing an arteriovenous aneurysm of the posterior parietal branch of the middle cerebral artery, close to the surface of the brain and draining into the longitudinal sinus by a large venous channel (Fig. 6). A parieto-occipital craniotomy was performed exposing a dilated vein containing mixed arterial and venous blood. A small knot of vessels lay just under the surface of the brain. When tantalum clips had been applied to the arterial supply of this angioma, arterial blood ceased to enter the large superficial vein. The patient was well in March, 1947.

Comment. This patient was thought at first to have an aneurysm in the Rolandic portion of the middle cerebral artery. The possibility of surgical treatment seemed so unlikely that several of her attending physicians preferred not to have angiograms made. Yet the exact location of the lesion which was shown to be most favorably placed for surgery could have been learned in no other way.

Case 3. A 52-year-old laundry worker entered the Peter Bent Brigham Hospital on Oct. 10, 1946, 2 weeks following an acute episode of nausea, vomiting and intense headache. Headache persisted and 12 days after the onset of symptoms diplopia and ptosis of the right eyelid appeared. At the time of admission the patient appeared to be somewhat confused and quite uncomfortable. The blood pressure was 210/130. There was complete paralysis of the right 3rd and 4th cranial nerves. Eyegrounds showed narrow arteries with nicking of the veins and,
on the left, several hemorrhages. The spinal fluid was xanthochromic. She improved steadily and on the 20th hospital day was scheduled for an angiogram at 2:30 p.m. Forty-five minutes earlier, while walking about the ward, she suddenly felt faint and returned to bed complaining of a stiff neck. The cerebrospinal fluid contained 100,000 erythrocytes per c. mm. Twenty-five days later, after complete clearing of the cerebrospinal fluid, she appeared entirely well except for the ophthalmoplegia which remained unchanged. A right common carotid arteriogram was made showing a large saccular aneurysm of the internal carotid artery at the level of the posterior communicating artery (Fig. 7). Just above this lesion on the posterior wall of the artery, an irregular arteriosclerotic plaque was outlined (Fig. 8). Seventeen days after the arteriogram the common carotid artery was ligated. In February of 1947 the eye signs had improved slightly and the patient appeared to be in good health despite her hypertension.

Comment. In the presence of hypertension an angiogram would not have been planned for this patient if the eye signs characteristic of aneurysm at the bifurcation of the internal carotid artery had not appeared. The occurrence of a second hemorrhage less than an hour before the scheduled angiogram presented a remarkable situation: if this had happened an hour, or even 24 hours later it would have been attributed to the diodrast injection, yet when the injection was made at a later date there were no untoward changes. The findings here are of great interest. The aneurysm is in a suitable position for a "trapping" operation. On the other hand, the finding of an arteriosclerotic plaque just above the lesion in the presence of hypertension...
formed a strong indication for conservative management. The detailed plan for this patient’s care rested largely upon the information learned through angiography.

SUMMARY

Nineteen years have passed since Moniz introduced cerebral angiography, yet, because of its technical difficulty and its possible danger to patients this diagnostic method has not come into general use.

Thorotrast has been the most widely employed contrast medium, although its dangers have been well known. Evidence is now beginning to appear in the literature that this material may cause sarcoma and other types of radiation damage in man as well as in experimental animals.

Diodrast (perabrodil) is a suitable medium for cerebral angiography. It is inert in the body, quickly excreted, and highly soluble. When large quantities of a concentrated solution are used in angiography reactions attributable to the hypertonicity of the solution may be encountered. To obviate the occurrence of reactions a method of injecting small quantities of dilute solutions of diodrast with a special angiogram needle is presented. In 25 successive operations, the patients ranged in age from 2 to 67 years, the diagnostic quality of the X-rays was satisfactory in all but 2; positive findings were frequent (9) and there were no undesirable effects.

Diodrast appears to be a safe contrast medium for cerebral angiography in both adults and children when used in this way. Roentgenograms of satisfactory quality are secured and several injections may be made for stereoscopic arteriograms, for anteroposterior projection, and for demonstration of two or more of the four arterial networks of the brain.

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