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STEREOTACTIC HEAVY-ION BRAGG PEAK RADIOSURGERY FOR INTRACRANIAL VASCULAR DISORDERS: METHOD FOR TREATMENT OF DEEP ARTERIOVENOUS MALFORMATIONS

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Stereotactic heavy-ion Bragg peak radiosurgery for intracranial vascular disorders: Method for treatment of deep arteriovenous malformations[1]

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ABSTRACT

The present paper represents the first clinical report for the use of stereotactically-directed narrow beams of helium ions from the 184-inch Synchrocyclotron at the Lawrence Berkeley Laboratory for the radiosurgical treatment of life-threatening vascular disorders of the brain, including inoperable or inaccessible deep arteriovenous malformations (AVMs) and carotid artery-cavernous sinus fistulas (CCFs). We describe the methods developed for stereotactic neuroradiological imaging and stereotactic helium-ion Bragg peak radiosurgery in the evaluation and treatment of the first 50 patients with deep AVMs in a clinical research protocol. We discuss the diagnosis and epidemiological characteristics of the diseases, the neurosurgical and radiosurgical methods of treatment available and the initial experience of stereotactic helium-ion Bragg peak radiosurgery, including stereotactic neuroradiological evaluation, treatment planning, heavy-ion beams, patient treatment protocol, early clinical results, patient evaluation and follow-up studies planned, and conclusions thus far obtained.

INTRODUCTION

Intracranial arteriovenous malformations (AVMs) have been the object of investigation for over a century (Kunc, 1978; Nyström, 1978). However, deep intracranial arteriovenous malformations, including carotid artery-cavernous sinus fistulas (CCFs), have not been reported on or treated until the last two decades, primarily because of their variable symptoms, changeable pathoanatomical relationships, and inaccessibility to vascular brain surgery (Kunc, 1978). Recently developed neurological imaging and microsurgical techniques are now making certain of the deep AVMs potentially amenable to treatment. However, serious limitations to neurosurgical or interventional treatment may exist in the case of deep AVMs, because of size, location (poorly accessible or inaccessible), patient condition, or other factors which preclude surgery. Conventional radiotherapy as a method of induced thrombosis has been tried in the past (Johnson, 1975) but now has been generally abandoned as unsuccessful (Peret, 1975; Olivecrona and Ladenheim, J., 1957; Pool, 1962; French and Chou, 1969). Stereotactic charged particle Bragg peak radiosurgery holds considerable promise for the treatment of deep-seated, large, or surgically inaccessible AVMs (Leksell, 1971; Kjellberg, 1977; Kjellberg et al., 1978; 1983; Kunc, 1978; Nyström, 1978; Backlund, 1978; Steiner et al., 1978; Fabrikant et al., 1980, 1983; Lawrence, 1983).

This paper represents the initial clinical research report for the use of stereotactically-directed helium-ion beams from the 184-inch Synchrocyclotron at Lawrence Berkeley Laboratory, University of California, Berkeley, for the radiosurgical treatment of the first 45 patients with life-threatening intracranial vascular disorders, including deep AVMs and CCFs. This paper will be followed by a detailed report on the clinical observations in the patients thus far treated.

Diagnosis and Incidence

Deep AVMs may be both supra- and infratentorial. CCFs are extracerebral, but present similar circulatory and therapeutic conditions as deep AVMs. The incidence rate of known deep AVMs approaches one case per 100,000 annually for the whole population (Nyström, 1978). A fairly large number of deep AVMs escape diagnosis based on autopsy series; the actual incidence rate may be twice that expected. Deep AVMs comprise up to 35% of all intracranial AVMs; intraventricular and brainstem AVMs comprise 20% of deep AVMs, and inoperable deep AVMs comprise 27% of all intracranial AVMs. In children, deep AVMs can comprise as much as 1% of neuropediatric hospital admissions. About one-third of all deep AVMs are in the posterior fossa (Kunc, 1978; Nyström, 1978); deep AVMs comprise 55% of all AVMs situated there. Deep AVMs appear most frequently in males; about 75% of patients with deep AVMs develop symptoms before 40 years of age.

Mortality for all AVMs approaches 15%; it is much higher, perhaps approaching 25% for deep AVMs owing to the more dangerous sites and the higher frequency of bleeding from some deep AVMs. Morbidity, including hemorrhage, neurologic disability, paresis, ataxia, brain stem dysfunction, coma, and seizures, is often severe since deep AVMs are almost always located close to important brain structures. Hemorrhage occurs in up to 25% of patients; the incidence of severely neurologically disabled patients approaches 20%, although morbidity, as such, including severe intractable headaches, is very much higher (Kunc, 1978; Nyström, 1978).

True CCFs arise on the basis of intracavernous rupture of the internal carotid artery as a result of tears in the intracavernous branches of this artery; some 50-65% of cases have traumatic involvement (Kunc, 1978; Fabrikant et al., 1980). Spontaneous CCFs comprise 3.3% of all deep AVMs with subarachnoid hemorrhage (Kunc, 1978). Most patients suffer pulsating exophthalmos, chemosis, extraocular palsies, orbital or cephalic bruit, headache and facial pain. The 3rd, 4th and/or 6th cranial nerves are impaired in 50% of cases; the 7th and 8th cranial nerves are frequently involved. Raised intraocular pressure impairs visual acuity in about 50% of patients. Fatal bleeding occasionally occurs (Kunc, 1978; Nyström, 1978).

Treatment

Recent advances in neurodiagnostic and microsurgical techniques have made direct neurosurgical treatment of intracranial AVMs safer and more successful. Surgical treatment of AVMs involves total excision, where possible, or combined with ligation or intravascular occlusion of feeding arteries and shunting vessels (Kunc, 1978; Leksell, 1971). For deep-seated AVMs, including CCFs, surgical approaches are frequently too difficult and associated with significant risk of massive bleeding or severe neurological deficit, or failure of obliteration. Similar risks and complications are associated with electrothrombosis, cryocoagulation, balloon catheterization, and intravascular embolization with synthetic polymers (Kunc, 1978). If AVMs in the brain are inoperable, or where other factors preclude neurosurgery, certain radiosurgical techniques have been tried (see Szikla, 1979).

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Background

A general concept in radiobiology is that blood vessels may be injured by ionizing radiation leading to thrombosis and hemostasis (Rubin and Casarett, 1968; Fabrikant, 1972). A mechanism is postulated and would involve three sequential factors: (1) vascular injury, (2) deviation of blood flow from the normal blood flow pattern, and (3) increased platelet activity, increased activation of coagulation, decreased fibrinolytic activity, leading to thrombosis and hemostasis (Backlund et al., 1977). It appears that the small abnormal feeding or shunting vessels of an AVM possess hemodynamic flow conditions that differ from flow in normal vessels. Therefore, irradiation of these small shunting vessels may lead to thrombosis and hemostasis in the AVM with eventual complete obliteration.

In 1980, our first patient with an inoperable deep intracranial AVM* was treated with stereotactic heavy-ion Bragg peak radiosurgery using 230-MeV/u helium ions at the 184-inch Synchrocyclotron at Lawrence Berkeley Laboratory (Fabrikant et al., 1980). Since then, 50 patients with deep intracranial vascular disorders have been treated using helium-ion Bragg peak beams, and additional patients are presently planned.

METHODS

Stereotactic Heavy-Ion Treatment Planning

Considerable study has gone into the development of a stereotactic system for delivery of heavy-ion beams to intracranial AVMs (Lyman, 1983; Lyman and Chong, 1974; Lyman and Howard, 1977; Lyman et al., 1971, 1973, 1979, 1980, in press; Tobias et al., 1952, 1959; Chen et al., 1979; Budinger et al., 1977; Fabrikant et al., 1980, 1983, in press). The procedure begins with the fabrication of a vacuum-formed polysytrene head-holder adapted to a frame for immobilization of the patient during stereotactic cerebral angiography, stereotactic X-ray computerized tomography (CT), and stereotactic heavy-ion Bragg peak radiosurgery (Figs. 1,2,3). The modified Leksell stereotactic

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* In the remainder of this paper, AVM = deep-seated arteriovenous malformation of the brain.

frame (Leksell, 1971) is attached to the head-immobilization mask, and adapted to cerebral angiographic and X-ray CT equipment and to the patient-positioner at the 184-inch Synchrocyclotron. Stereotactic cerebral angiography and stereotactic CT brain scans are performed (Fig. 2). The CT data are transferred to a VAX 11/780 computer system in our laboratory for interactive charged particle treatment planning and provide the basis for stereotactically-directed helium-ion beams to AVM target contours. Entry angles and beam ports are chosen to confine the high-dose Bragg peak region to the defined target volume while carefully protecting adjacent normal brain structures. Stereotactic radiosurgical treatment planning programs use the CT data on a pixel-by-pixel basis to (a) design and/or select a collimator aperture for each entry portal, (b) select the appropriate spread Bragg peak for helium-ion radiation, (c) design appropriate compensators to contour the stopping region of the helium-ion beams, and (d) generate isoeffect and physical dose-distributions overlayed on the CT image for adaptation to stereotactic radiosurgical treatment with accelerated heavy ions.

Heavy-Ion Beams

A new beamline configuration for stereotactic radiosurgery in the brain with the Bragg ionization peak of the 230-MeV/u helium-ion beam at the 184-inch Synchrocyclotron has been developed (Lyman et al., in press). This modified beam has a 14.7 cm range in water to the Bragg peak, with sharply delimited lateral and distal borders. The practical limits on beam diameter range from 0.6 cm to 4.0 cm (Fig. 4). The unmodulated Bragg peak maximum dose is greater than 3 times the entrance dose and the width of the peak at 80% of the maximum is 0.7 cm. The range of the helium-ion beam can be modulated by a rotating acrylic variable thickness absorber to increase the width of the high dose region to as much as 4.0 cm. The physical properties of this beam are similar to those of the proton beams that have been available for stereotactic radiosurgery at the Harvard Cyclotron Laboratory (Koehler et al., 1974; Kjellberg, 1977; Kjellberg et al., 1978) and at the Gustaf Werner Institute at the University of Uppsala (Larsson, 1980; Larsson and Sarby, 1974). The maximum range of the 230-MeV/u helium-ion beam is greater than that of these proton beams; therefore, more energy degradation is necessary to obtain the same residual range. Since the nuclear charge and mass of helium is larger than the proton, the multiple scattering and the range straggling can be less for the same residual range in tissues.

This helium-ion beam has proven suitable for neuroscience research to induce focal lesions in the central nervous system (Fabrikant et al., 1980). It provides good dose-localization and dose-distribution for stereotactic helium-ion radiosurgery in all patients with AVMs, including CCFs, thus far treated. Studies are in progress to develop beam characteristics of heavier ions, such as carbon ions with small uniform transverse profile and modified Bragg peak for improved dose-distribution at the Bevalac. These heavier-ion beams have physical characteristics with unique advantages for application to stereotactic Bragg peak radiosurgery of the central nervous system (Budinger et al., 1977; Fabrikant et al., 1980).

Patient Treatment

Treatment with helium-ion beams is based on the individual computerized treatment planned stereotactically-directed heavy-ion beam dose-distribution calculated from stereotactic X-ray CT scans and stereotactic cerebral angiograms (Lyman et al., in press; Fabrikant et al., 1983; in press). Necessary minor corrections of the X, Y and Z coordinates are made during simulation. The patient's head is secured to the ISAH system (Irradiation Stereotactic Apparatus for Humans) at the 184-inch Synchrocyclotron by the polystyrene head-immobilizer (Lyman et al., in press; Lyman and Chong, 1974; Tobias, 1980; Lawrence, 1983; in press). Computer-controlled head-, body-, and beam-positioning can place the collimated beam to within 0.1 mm as desired (Lyman and Chong, 1974; Tobias, 1980).

The central AVM dose, the aperture size, the number of ports, the angulation of the delivered helium-ion beams, and the spread Bragg peak all determine the isodose contour. Presently, total doses of 45 Gy equivalent (GyE) are delivered to treatment volumes of up to 25,000 mm^3; the smallest volumes treated with the unmodified Bragg peak are about 120 mm^3, and the average volumes treated for most patients are in the range of 1500 mm^3 to 5000 mm^3. Treatment occurs through 1 to 6 entry portals, delivered daily for 1 to 3 days, depending on the treatment volume, and the volume of normal brain tissue traversed by the beam. Irradiation times per portal range from 1 to 4 minutes (Lyman et al., in press). The dose to the critical normal brain structures immediately surrounding the AVM is considerably less than 45 GyE; fall-off to 10% of the central dose occurs within 4-6 mm, and is much sharper (within 2-3 mm) along the lateral margins of the helium-ion beam (Lyman et al., in press) (Figs. 2, 3, 4, 5).

RESULTS

Stereotactic cerebral angiography and stereotactic CT brain scanning are carried out prior to stereotactic radiosurgery and at selected intervals following radiosurgery. Extended follow-up to 36 months is now done on a regular basis, and 48 to 60 months is planned for each patient as necessary. Clinical objectives are to achieve changes in the intracerebral hemodynamic condition resulting in a decrease in frequency of hemorrhages, in neurological deficiencies, subjective complaints including headaches, or in frequency of seizures. Initial observations in all 45 patients thus far treated indicate that these objectives are being achieved. There have been no neurologic complications of radiation damage to the normal brain tissue; thus far, no evidence of brain injury or progressive or fixed neurological deficiencies have occurred as a result of the stereotactic radiosurgical procedure. Radiological objectives are to achieve hemodynamic changes, e.g., decrease in blood flow through the AVM with decrease in the size of the AVM until total disappearance (Figs. 3, 6, 7). It has been observed both by the Karolinska group (Backlund, 1980; Steiner, personal communication) and the Harvard group (Kjellberg, personal communication) that hemodynamic changes occur progressively and are usually present before morphological vascular alterations. Since it may require up to 12 to 18 months before initial changes occur, and not be completed in some instances before 24 months, and since most patients in our clinical research study have been treated within the past 18 months, it is not possible to provide observations on long-term follow-up at this time. However, in 7 patients, significant decrease in size of and the rate of blood flow through the treated AVM has already occurred (Figs. 6, 7). In one patient with a CCF, the fistula was completely obliterated at 3 months, and her pulsating exophthalmos, headache, and visual disturbances are completely relieved (Fig. 3).

Patient Evaluation and Follow-Up

During the next four years, studies on treated AVM brain patients will emphasize the results of stereotactic heavy-ion Bragg peak radiosurgery with time. (1) Neurological condition. Patients most frequently present with one or more of the following clinical features: hemorrhage, seizure, headache, neurological deficits, and mental deficits. The extent to which the changes in the hemodynamic condition following treatment of the AVM may result in decrease of neurological deficiencies, subjective complaints, frequency of seizures, etc., will be evaluated. (2) Radiological studies. Cerebral angiography, X-ray CT scanning and certain special investigative studies (e.g., positron emission tomography (PET) and/or single photon emission computed tomography (SPECT) scanning and nuclear magnetic resonance (NMR) scanning) are being carried out or planned for all patients prior to stereotactic radiosurgery, and at intervals following treatment (Fig. 8). The following changes, if present, will be quantitated. (a) Hemodynamic changes, e.g., decrease in blood volume and flow through the AVM with decrease in size of the feeder arteries and shunting vessels and draining veins. These changes may be best quantitated with PET and/or NMR scans, or digital radiography which may measure blood flow changes more accurately. (b) Anatomical changes, e.g. progressive decrease in the size of the AVM until total disappearance, potential transient or permanent disturbances in myelination processes, leading to demyelination, and early and late delayed radiation-incuded injury in the brain (Sheline et al., 1980). As yet, no disturbances of myelination processes have been observed in any of our patients thus far treated with stereotactically-directed helium-ion beams.

DISCUSSION

Stereotactic Radiosurgery

Leksell, Steiner, Backlund and their colleagues (Leksell, 1971; Backlund, 1978; Backlund et al., 1978; Steiner et al., 1978; Norén, 1982) at the

Karolinska Sjukhuset, Stockholm have introduced stereotactic radiosurgery of AVMs using focused gamma beams from a specially-designed unit with 179 cobalt-60 sources, stereotactically-directed at a volume less than 2.5 cm diameter within the brain. Patients receive a single treatment; presently doses of approximately 50 Gy are delivered (Steiner, personal communication). In their series of 135 patients thus far treated, in the group in which the entire AVM was included in the irradiated field, 81 patients have now gone through one year, and 63 patients through two years of follow-up. When the AVMs were completely covered by the radiation field, over 95% of the patients benefited from a partial or complete cure. Total obliteration of the AVM has occurred in about 85% of patients by 2 years (Steiner, personal communication). Partial recovery, presumably with progress to total obliteration in the future, occurred in 10%. However, this focused gamma irradiation is limited in its isodose distribution and size of treatment volume, primarily due to physical characteristics of the equipment and beam quality (Larsson and Sarby, 1974; Larsson, 1980). Barcia-Salorio (Barcia-Salorio et al., 1977) at the University of Valencia, Spain, has begun to use a cobalt-60 teletherapy beam to induce focal lesions in AVMs.

Initial studies on the feasibility of proton beam-induced narrow focal lesions in the brain were carried out by Larsson (see review, Larsson, 1980) at the Gustaf Werner Institute Uppsala 185 MeV cyclotron. Kjellberg (1977; Kjellberg et al., 1978; 1983) introduced stereotactic proton-beam Bragg peak radiosurgery of AVMs at the Harvard 165 MeV cyclotron. The proton beam is used to treat a larger range of sizes of AVMs than is possible with the Karolinska gamma unit. Patients receive a single treatment to appropriate tissue volumes; presently doses used are varied (range 9 to 50 Gy), depending on the brain volume irradiated. The Harvard group has now treated 293 patients (Kjellberg, personal communication), and has reported on the follow-up of the first 75 patients treated (Kjellberg, et al., 1983). All patients were considered inoperable, either because of size of the AVM, or the excessive risk of excision. In their series, no patients have died from hemorrhage after a 15-month period following radiosurgery, or as a complication of the radiosurgical treatment; in 75 patients with 2-16 year follow-up, 87% have thus far demonstrated some reduction in the size of the AVM, and 20% have demonstrated complete obliteration of the AVM (Kjellberg, et al., 1983)

Future Studies

Research in our laboratory in stereotactic heavy-ion Bragg peak radiosurgery for intracranial deep-seated neurovascular disorders in brain patients is designed: (1) to introduce technical modifications and improvements of the radiosurgical technique---including stereotactic neuroradiological studies for quantitating radiation changes in the brain, computer-based interactive treatment planning, and heavy-ion beam-delivery and dose-distribution---to achieve a safe and reliable therapeutic procedure; (2) to evaluate the long-term results in patients treated with helium ions for AVMs of the brain and spinal cord; (3) to develop the method using accelerated heavy ions (Bragg peak beams) at the Bevalac for all brain patients for improved biological and physical effects, using carbon ions or possibly heavier ions. The advantages of heavier ions over helium ions and protons include narrow beams with less range straggling and less multiple scattering for the same residual range in tissues, and improved dose-distribution in the Bragg peak, with very sharp lateral and distal borders, and with greater sparing of critical structures in adjacent CNS tissues in the brain and spinal cord. The carbon-ion beam also provides a carbon-11 ion radioactive beam which is presently being investigated for achieving precise localization of the stopping points of the beam inside the brain (Tobias, 1983; in press; Tobias et al., 1971; Chatterjee et al., 1981; Fabrikant et al., 1980; Lawrence, 1983; in press). And (4) to perfect the method at the Bevalac for application at the clinical level when medical accelerators are more generally available throughout the world (Alpen, 1983).

CONCLUSIONS

Certain conclusions can be drawn on review of the first 3 years of the use of stereotactic helium-ion Bragg peak radiosurgery for inoperable AVMs of the brain at the 184-inch Synchrocyclotron at Lawrence Berkeley Laboratory.

(1) Whenever possible, conventional surgical excision remains the treatment of choice for AVMs of the brain. In certain situations, interventional neuroradiological intravascular embolization in conjunction with surgical excision may prove advantageous (Backlund, 1980; Hosobuchi et al., 1982). When AVMs are inaccessible and conditions preclude surgery and/or embolization, stereotactic heavy-ion Bragg peak radiosurgery, (alone, or in combination with partial surgical ligation and/or excision, and/or intraluminal embolization of large feeder vessels) appears to be a safe, reliable, and potentially efficient alternative. It is presently used in our laboratory as the definitive form of treatment, either alone, or in combination with and following neurosurgical vascular ligation of the only accessible arterial feeders, or interventional neuroradiological intravascular embolization of larger arterial vessels. Kjellberg (Kjellberg et al., 1983) has stated that his experience compels the conclusion that virtually all AVMs of the brain can be treated with stereotactic charged particle Bragg peak radiosurgery.

(2) Stereotactically-directed heavy-ion Bragg peak radiosurgery is more advantageous than gamma beams or proton beams because of improved spatial definition and dose-distribution within the AVM target volume in the brain. (3) Experience demonstrates that therapeutic failure results from irradiating some, but not all, of the multiple arterial feeder shunts of the AVM, or where only a part of the pathological cluster of vessels is irradiated. This has not occurred with our use of helium-ion Bragg peak beams and our dose-localization and dose-distributions. (4) Initial therapeutic results demonstrate that heavy-ion focal irradiation of the AVM can induce hemodynamic changes and neurovascular obliteration associated with reduction in the size and in flow leading to complete obliteration of the vascular abnormality (Figs. 3, 6, 7). Neurological changes with improvement have been observed within periods as short as 3 months; cerebral angiographic changes with decreased AVM size and flow have been observed within 6 months following irradiation. However, most pathologic changes require more than a year to occur and may extend over a 1-to-2 year period.

(5) The stereotactic heavy-ion radiosurgical method can prove to be a highly selective one for treatment of surgically-inaccessible structures within the brain. Its advantages are: (a) it is a safe, noninvasive procedure without any blood loss; (b) patients under threat of hemorrhage from inoperable or inaccessible AVMs can be treated in cases where neurosurgery is unable to help; and (c) prolonged hospitalization is not required; all our patients are treated on an ambulatory basis. (6) The disadvantages of the method are: (a) radiographic evidence of change within the AVM does not begin before some 6 months, and frequently obliteration requires 12 to 18 months or more; thus, patients

are not protected and are under threat of hemorrhage for a long time; (b) time-dose-volume-fractionation relationships for heavy-ion focal irradiation of brain and other CNS tissues are not fully understood. Experience with gamma beams and proton beams indicate that for large AVMs in functionally important brain regions, when large doses of radiation or large radiation fields have to be applied, there exists the danger of serious brain damage and neurological deficits (for review, Sheline et al., 1980). This has not occurred in our experience using stereotactically-directed narrow beams of helium-ions. However, much research must be done---at the tissue and animal levels, and on heavy-ion beam quality and dosimetry establishing a firm scientific basis for LET/RBE relationships in the cells and tissues of the central nervous system---for this method of stereotactic heavy-ion Bragg peak radiosurgery to offer the possibility of complete recovery and with no late sequelae in patients with deep-seated AVMs.

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REFERENCES

ALPEN, E. L., 1983. The Heavy Ion Medical Accelerator. Preliminary Design Summary. Lawrence Berkeley Laboratory Report PUB 5097 (University of California, Berkeley).

BACKLUND, E. O., 1982. Stereotactic radiosurgery in intracranial tumors and vascular malformations. Advances and Technical Standards in Neurosurgery. Ed. by H. Krayenbuhl, (Springer-Verlag, Vienna), 6, 3-37.

BACKLUND, E. O., ARDT, J., DAHLEN, T. G., LEKSELL, L. & STEINER, L., 1978. Radiosurgery in intracranial arteriovenous malformations. I. Technique. In Neurological Surgery with Emphasis on Non-invasive Methods of Diagnosis and Treatment. Ed. by R. Carrea and D. LeVay (Excerpta Medica, Amsterdam), pp. 162-167.

BARCIA-SALORIO, J. L., HERNANDEZ, G., BROSTA, J., BALLESTER, B. & MASBOUT, G., 1977. Radiosurgical treatment of a carotid-cavernous fistula. In Stereotaxic Cerebral Irradiation. Ed. by G. Szikla (INSERM Symposium No. 12, Amsterdam), pp. 251-256.

BUDINGER, T. F., LINFOOT, J. A., MOYER, B. R., LYMAN, J. T. & PELLETIER, T. L., 1977. Brain research with heavy-ion beams. In Biological and Medical Research with Accelerated Heavy Ions at the Bevalac 1974-1977. Lawrence Berkeley Laboratory Report LBL-5610 (University of California, Berkeley), pp. 187-197.

CHATTERJEE, A., ALPEN, E. L., TOBIAS, C. A., LLACER, J. & ALONZO, J., 1981. High energy beams of radioactive nuclei and their biomedical applications. International Journal of Radiation Oncology, Biology and Physics, 7, 503-507.

CHEN, G.T.Y., SINGH, R. P., CASTRO, J. R., LYMAN, J. T. & QUIVEY, J. M., 1979. Treatment planning for heavy ion radiotherapy. International Journal of Radiation Oncology, Biology and Physics, 5, 1809-1819.

FABRIKANT, J. I., 1972. Radiobiology (Year Book Medical, Chicago).

FABRIKANT, J. I., BUDINGER, T. F., TOBIAS, C. A. & BORN, J. L., 1980. Focal lesions in the central nervous system. In Biological and Medical Research with Accelerated Heavy Ions at the Bevalac 1977-1980. Ed. by C. A. Tobias and M. C. Pirruccello, Lawrence Berkeley Laboratory Report LBL-11220 (University of California, Berkeley), pp. 399-405.

FABRIKANT, J. I., LYMAN, J. T. & HOSOBUCHI, Y., 1983. Stereotactic heavy-ion Bragg peak radiosurgery for intracranial vascular disorders. In Heavy Particle Irradiation of Intracranial Lesions. Ed. by J. H. Lawrence, Lawrence Berkeley Laboratory Report No. LBL-16011 (University of California, Berkeley), pp. 35-42.

FABRIKANT, J. I., LYMAN, J. T. & HOSOBUCHI, Y., in press. Stereotactic heavy-ion Bragg peak radiosurgery for intracranial vascular disorders. In Heavy Particle Irradiation of Intracranial Lesions. Ed. by J. H. Lawrence. To be published in Neurosurgery. Ed. by R. H. Wilkins and S. S. Rengcharry (McGraw Hill, New York).

FRENCH, L. A. & CHOU, S. N., 1969. Conventional methods for treating intracranial arteriovenous malformations. Progress in Neurological Surgery, 3, 274-391.

HOSOBUCHI, Y., FABRIKANT, J. I. & LYMAN, J. T., 1982. Stereotactic radiosurgery for intracranial vascular disorders. (ab) (Western Neurosurgical Society, San Francisco), p. 1.

JOHNSON, R. T. Radiotherapy of cerebral angiomas. With a note on some problems on diagnosis. In Cerebral Angiomas. Advances in Diagnosis and Therapy. Ed. by H. W. Pia, J. R. W. Gleave, E. Grote and J. Zierski (Springer-Verlag, New York), pp. 256-267.

KJELLBERG, R. M., 1977. Stereotactic Bragg peak proton radiosurgery results. In: Stereotaxic Cerebral Irradiation. Ed. by G. Szikla (INSERM Symposium No. 12, Amsterdam), pp. 233-240.

KJELLBERG, R. M., POLETTI, C. E., ROBERSON, G. H., & ADAMS, R. D., 1978. Bragg peak proton beam treatment of arteriovenous malformations of the brain. In Neurological Surgery with Emphasis on Non-invasive Methods of Diagnosis and Treatment. Ed. by R. Carrea and D. LeVay (Excerpta Medica, Amsterdam), pp. 184-187.

KJELLBERG, R. M., 1983. Bragg-peak proton-beam therapy for arteriovenous malformations of the brain. New England Journal of Medicine, 309, 269-274.

KOEHLER, A. M., SCHNEIDER, R. J. & SISTERSON, J. M., 1975. Range modulators for protons and heavy ions. Nuclear Instruments and Methods, 131, 437-440.

KUNC, Z., 1978. Deep-seated arteriovenous malformations: A critical review. In Neurological Surgery with Emphasis on Non-Invasive Methods of Diagnosis and Treatment. Ed. by R. Carrea (Excerpta Medica, Amsterdam), pp. 188-193.

LAWRENCE, J. H., 1983. Heavy particle irradiation of intracranial lesions. Lawrence Berkeley Laboratory Report LBL-16011, (University of California, Berkeley). In Neurosurgery. Ed. by R. H. Wilkins and S. S. Rengcharry (McGraw-Hill, Philadelphia), in press.

LEKSELL, L., 1971. Stereotaxis and Radiosurgery--An Operative System. (Charles C. Thomas, Springfield).

LYMAN, J. T., 1983. Computer modeling of heavy charged particle beams. In Pion and Heavy-Ion Radiotherapy. Pre-clinical and Clinical Studies. Ed. by L. D. Skarsgard (Elsevier Biomedical, New York), pp. 139-147.

LYMAN, J. T., CHEN, G. T. Y., KANSTEIN, L. & HOWARD, J., 1979. Heavy particle facilities at the Lawrence Berkeley Laboratory. In Proceedings of the First International Seminar on the Uses of Proton Beams in Radiation Therapy (Atomistadt, Moscow), 2, 122-134.

LYMAN, J. T. & CHONG, C. Y., 1974. ISAH: A versatile treatment positioner for external radiation therapy. Cancer 34, 12-16.

LYMAN, J. T. & HOWARD, J., 1977. Dosimetry and instrumentation for helium and heavy ions. International Journal of Radiation Oncology, Biology and Physics, 3, 81-85.

LYMAN, J. T., HOWARD, J., KANSTEIN, L. & ALONZO, J. R., 1980. Radiological physics of heavy charged particle beams used for therapy. In Biological and Medical Research with Accelerated Heavy Ions at the Bevalac 1977-1980. Ed. by C.A. Tobias and M. C. Pirruccello, Lawrence Berkeley Laboratory Report LBL-11220 (University of California, Berkeley), pp. 319-324.

LYMAN, J. T., HOWARD, J., MACCABEE, H. D., RAJU, M. R., SPERINDE, J., WALTON, R., WELCH, C. P. & TOBIAS, C. A., 1971. Experimental set-up and physical measurements of a heavy-ion beam for initial biological irradiation at the Bevatron. In Initial Radiobiological Experiments with Accelerated Nitrogen Ions at the Bevatron. Lawrence Berkeley Laboratory Report LBL-529 (University of California, Berkeley), p. 1-19.

LYMAN, J. T., HOWARD, J., WELCH, G. P., SCHIMMERLING, W. & TOBIAS, C. A., 1973. Experimental set-up and physical measurements of the heavy-ion beams used for biological irradiations. In Radiobiological Experiments Using Accelerated Heavy Ions at the Bevatron. Lawrence Berkeley Laboratory Report LBL-2016 (University of California, Berkeley), pp. 100-111.

LYMAN, J. T., KANSTEIN, L., YEATER F., FABRIKANT, J. I. & HOSOBUCHI, Y. A helium ion beam for stereoetactic radiosurgery. American Journal of Neuroradiology, in press.

NOREN, G., 1982. Stereotactic Radiosurgery in Acoustic Neuromas. A New Therapeutic Approach (Karolinska Sjukhuset, Stockholm).

NYSTROM, S. H. M., 1978. Epidemiology and clinical diagnosis of deep intracranial arteriovenous malformations including carotid-cavernous fistulas. In Neurological Surgery with Emphasis on Non-Invasive Methods of Diagnosis and Treatment. Ed. by R. Carrea and D. LeVay (Excerpta Medica, Amsterdam), pp. 188-193.

OLIVECRONA, H. & Ladenheim, J., 1957. Arteriovenous Malformations of the Carotid and Vertebral Artery Systems. (Springer-Verlag, Berlin).

PERRET, G. E., 1975. Conservative management of inoperable arteriovenous malformations. In Cerebral Angiomas. Advances in Diagnosis and Therapy. Ed. by H. W. Pia, J. R. W. Gleave, E. Grote, J. Zierski (Springer-Verlag, New York), pp. 268-270.

POOL, J. T., 1962. Treatment of arteriovenous malformations of the cerebral hemispheres. Journal of Neurosurgery, 19, 136-141.

RUBIN, P. & CASARETT, G. W., 1968. Clinical Radiation Pathology. (Saunders, Philadelphia).

SHELINE, G. E., WARA, W. M. & SMITH, V., 1980. Therapeutic irradiation and brain injury. International Journal of Radiation Oncology, Biology and Physics, 6, 1215-1228.

STEINER, L., BACKLUND, E. O., GREITZ, T., LEKSELL, L., NORÉN, G. & RAHN, T., 1978. Radiosurgery and intracranial arteriovenous malformations. Neurological Surgery with Emphasis on Non-Invasive Methods of Diagnosis and Treatment. Ed. by R. Carrea and D. LeVay (Excerpta Medica, Amsterdam).

SZIKLA, G., Ed., 1979. Stereotactic Cerebral Irradiation (Elsevier/North Holland Biomedical Press, Oxford).

TOBIAS, C. A., 1973. Pretherapeutic investigations with accelerated heavy ions. Radiology, 108, 145-158.

TOBIAS, C. A., 1980. Pituitary irradiation: Radiation physics and biology. In Recent Advances in the Diagnosis and Treatment of Pituitary Tumors. Ed. by J. A. Linfoot (Raven Press, New York), pp. 221-253.

TOBIAS, C. A., ANGER, H. O. & LAWRENCE, J. H., 1952. Radiologic use of high energy deuterons and alpha particles. American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 67, 1-27.

TOBIAS, C. A., CHATTERJEE, A. & SMITH, A. R, 1971. Radioactive fragmentation of N^{7+} ion beams observed in a beryllium target. Physics Letters, A, 37, 119-120.

TOBIAS, C. A., VAN DYKE, D. C., SIMPSON, M. E., ANGER, H. O., HUGG, R. L. & KNOEFF, A. A., 1959. Irradiation of the pituitary of the rat with high-energy deuterons. American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 72, 1-21.

FIGURE LEGENDS

Fig. 1. Stereotactic cerebral angiogram for stereotactic helium-ion Bragg peak radiosurgery of a left cerebral (frontal) AVM in a 45-year-old woman. (A) and (B): AP and lateral views demonstrating the AVM filling primarily from the left anterior cerebral artery supply (arrows). The patient is immobilized in the stereotactic head mask and frame. (C) and (D); subtraction images of the stereotactic cerebral angiograms demonstrating the size, shape, and location of the AVM in the left frontal pole of the cerebral cortex (arrows). (XBB 824-3973A)

Fig. 2. Stereotactic helium-ion Bragg peak radiosurgery of the AVM illustrated in Figure 1. (A): stereotactic CT scan of the brain demonstrating the contrast accumulation in the left frontal AVM. (B): AP localization radiograph of the skull illustrating isodose curves of the stereotactic radiosurgical treatment plan. (C): lateral localization radiograph and isodose curves of the treatment plan. Multiple-port radiosurgery was delivered over 2 days; the dose was 45 GyE, and the volume of tissue receiving greater than 40 GyE is estimated to be 1440 mm^3. (XBB 828-7006)

Fig. 3. Stereotactic helium-ion Bragg peak radiosurgery of a right CCF in a 67-year-old woman. (A) and (B): subtraction X-ray images (AP and lateral views) of stereotactic cerebral angiogram demonstrating the location and size of the right CCF (arrows); the patient is immobilized in the stereotactic head mask and frame. (C): AP localization radiograph with the isodensity contours of the stereotactic radiosurgical treatment plan. (D): lateral localization

radiograph demonstrating the 6-mm-diameter helium-ion beam port. Multiple-port radiosurgery was delivered in 1 day; the dose was 40 GyE, and the volume of tissue receiving greater than 60 percent of the dose is estimated to be 280 mm^3. (XBB 800-12345A)

Fig. 4. The 230-MeV/u helium-ion beam can be modified to adapt to a variety of radiosurgical conditions. This is an example of the Bragg ionization curve and its transverse profile for stereotactic radiosurgery of an intracranial vascular disorder at 6 cm depth (see Figure 3). (XBL 828-1107)

Fig. 5. Isodose contour, stereotactic helium-ion Bragg peak radiosurgery of a brain stem AVM in a 30-year-old male. The beam was collimated by a 10 mm x 8.5 mm elliptical aperture; treatment was carried out using two ports, anterior and posterior, in one day to a volume of 700 mm^3 within the brain stem. (BBC 835-4438)

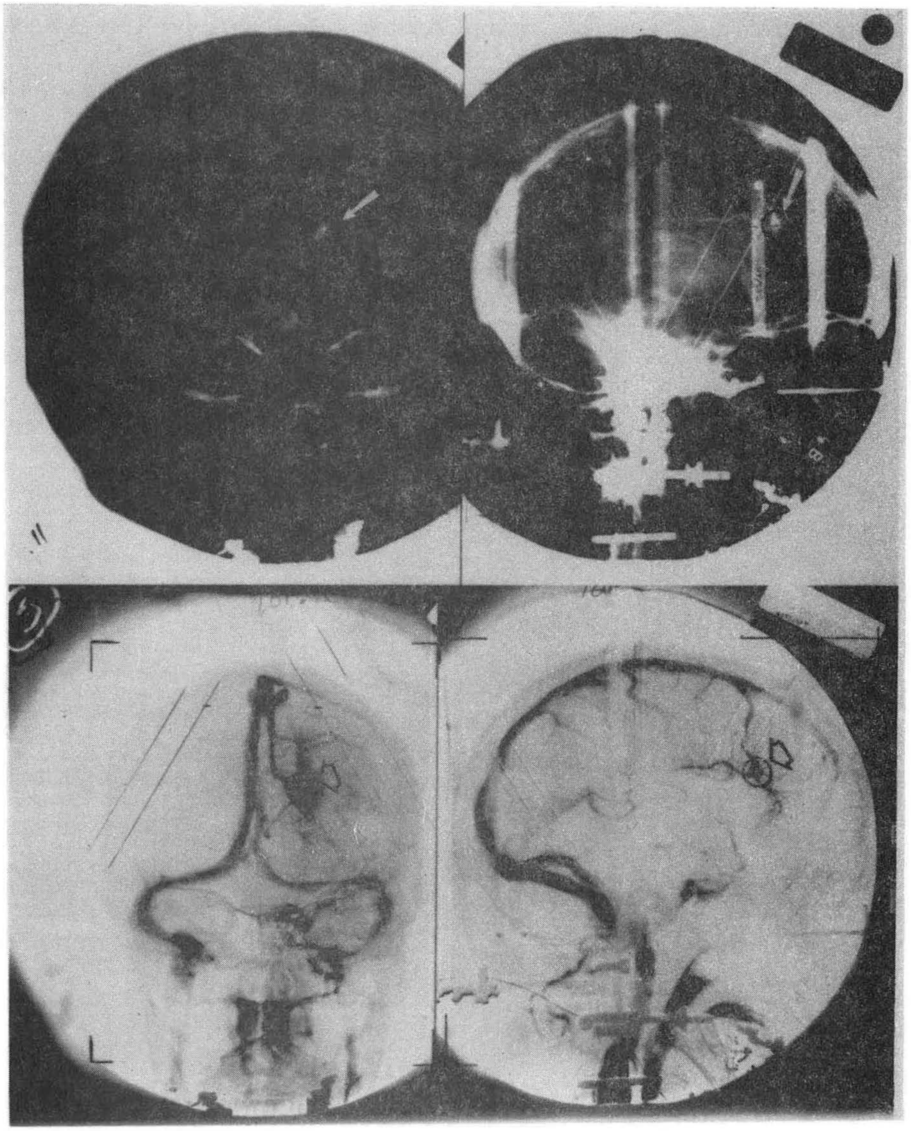
Fig. 6. (A). Patient is a 40-year-old male with large right cerebral (parietooccipital) AVM; marked visual field defects, severe intractable headaches, and repeated episodes of subarachnoid hemorrhages. Cerebral angiogram, April 1982, demonstrating the size, shape and location of the AVM and the three feeding vessels originating off the right posterior communicating artery. (B) Cerebral angiogram, May 1982; reduction in size of the AVM following surgical clipping of the accessible arterial feeders. The size, shape and location of the residual AVM is demonstrated. The patient was treated with stereotactic helium-ion Bragg peak radiosurgery, 4 ports,

4 fractions in 4 days, 45 GyE, to a volume of 15,000 mm^3. (C) Cerebral angiogram, May 1983, 1 year after radiosurgery; obliteration of arterial feeding and shunting vessels. Only large draining veins remain which collect near-normal blood flow. No hemorrhages have occurred since stereotactic radiosurgery; severe headaches rarely occur. (XBB 836-5168A)

Fig. 7. (A) Patient is a 60-year-old female who had repeated seizures and severe headaches, neurologic deficits of mild disorientation, left leg spasticity and gait ataxia. Stereotactic cerebral angiogram demonstrated a large right cerebral (frontoparietal) AVM. (B) Radiosurgical treatment was carried out in January, 1981, 2 ports, 4 fractions in 4 days, 45 GyE. Cerebral angiogram, May 1981; AVM decreased approximately 50% in size with a large reduction in blood flow confirmed by CT scans. (C) Cerebral angiogram, March 1982, 14 months after radiosurgical treatment; obliteration of all arterial feeders and shunting vessels of the AVM. Patient has had no further seizures, and her headaches have decreased considerably in intensity and frequency. Her neurologic deficits have all markedly improved. (XBB 836-5167B)

Fig. 8. Right cerebral AVM localization and blood flow dynamics using rubidium-82 and positron emission tomography (PET) with the Donner 280-crystal ring. The AVM is seen extending into the thalamus and cerebral cortex. Because rubidium-82 is a positron emitter, transverse sections showing changes in isotope distribution can be obtained, using coincidence detection of the annihilation photons produced by the positrons. PET thus provides a valuable quantitative method for investigating changes in blood flow dynamics before and

after stereotactic Bragg peak radiosurgery. The illustration is reproduced from computer-synthesized color images depicting blood flow rates and intensities. (From the Positron Emission Tomography Research Medicine Laboratory of Professor T. F. Budinger). (CBB 818-7343).



XBB 824-3973A

Figure 1

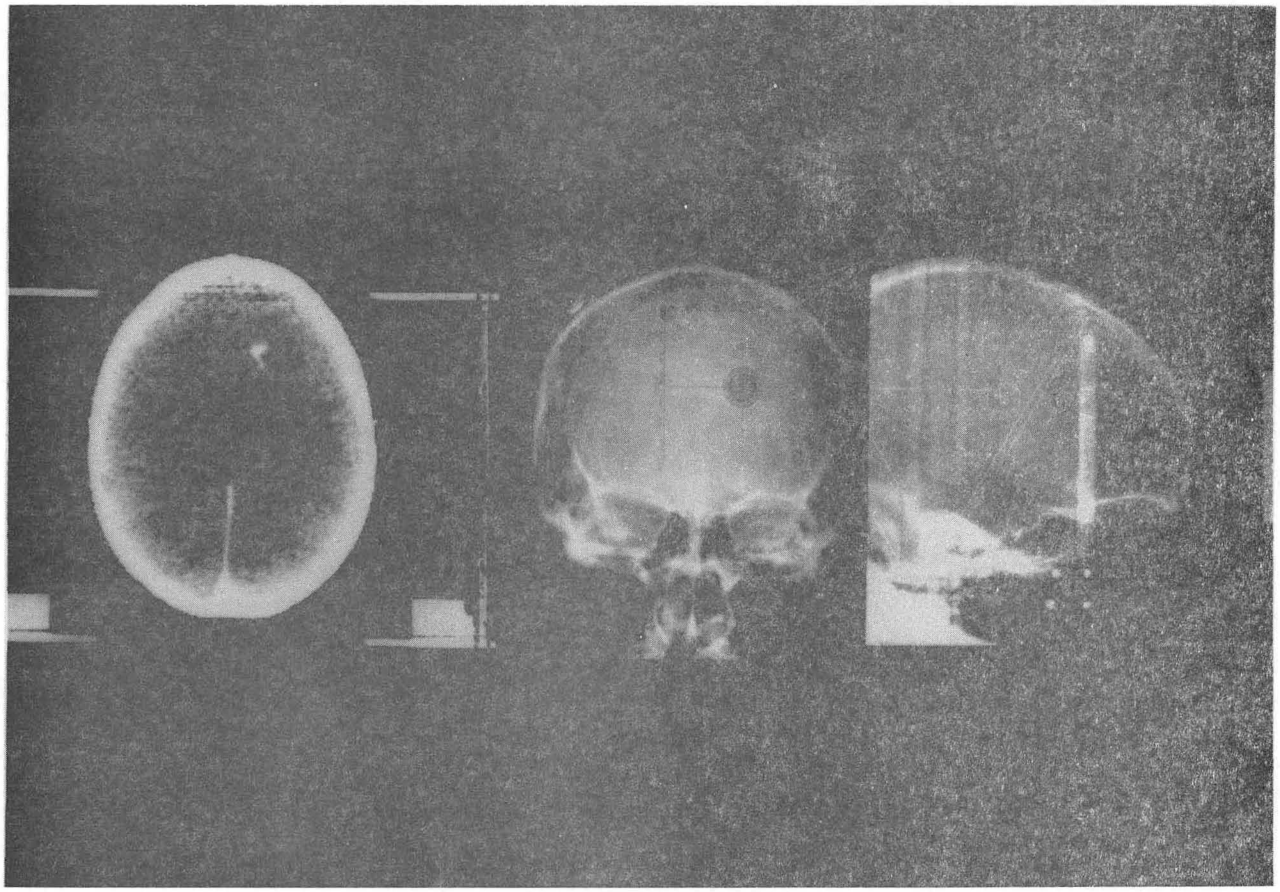


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Figure 2

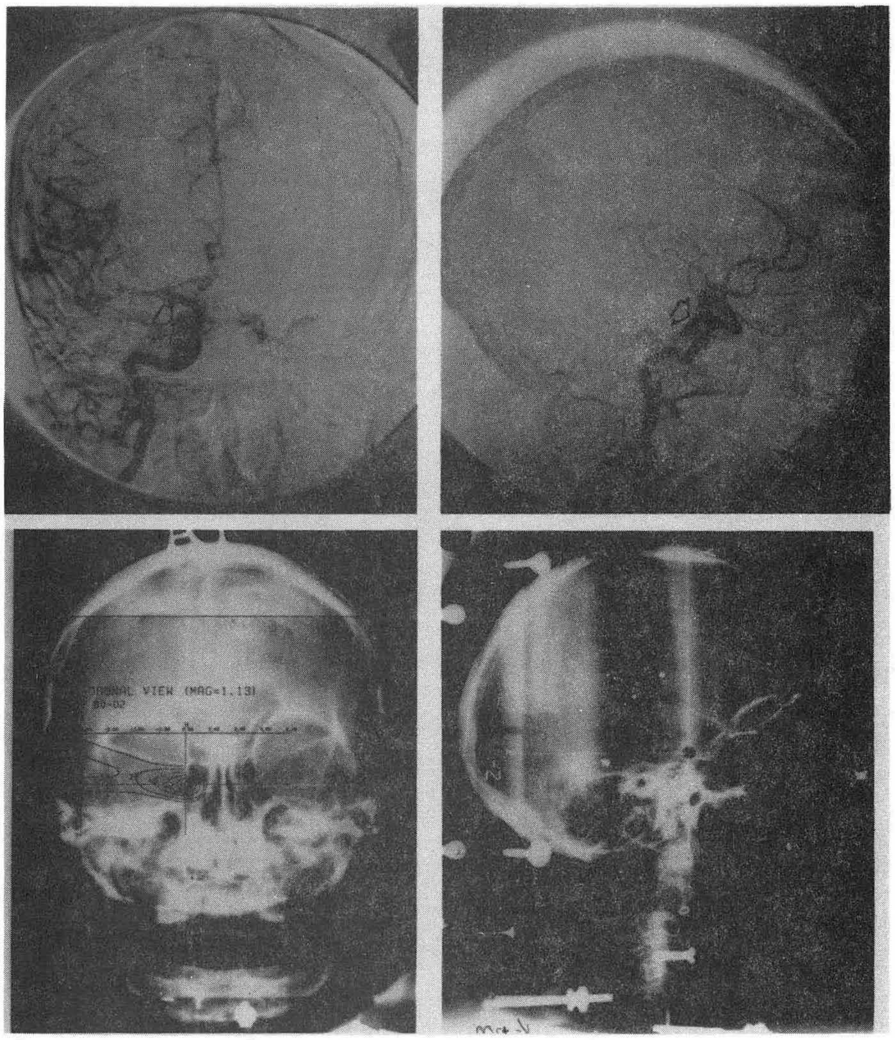

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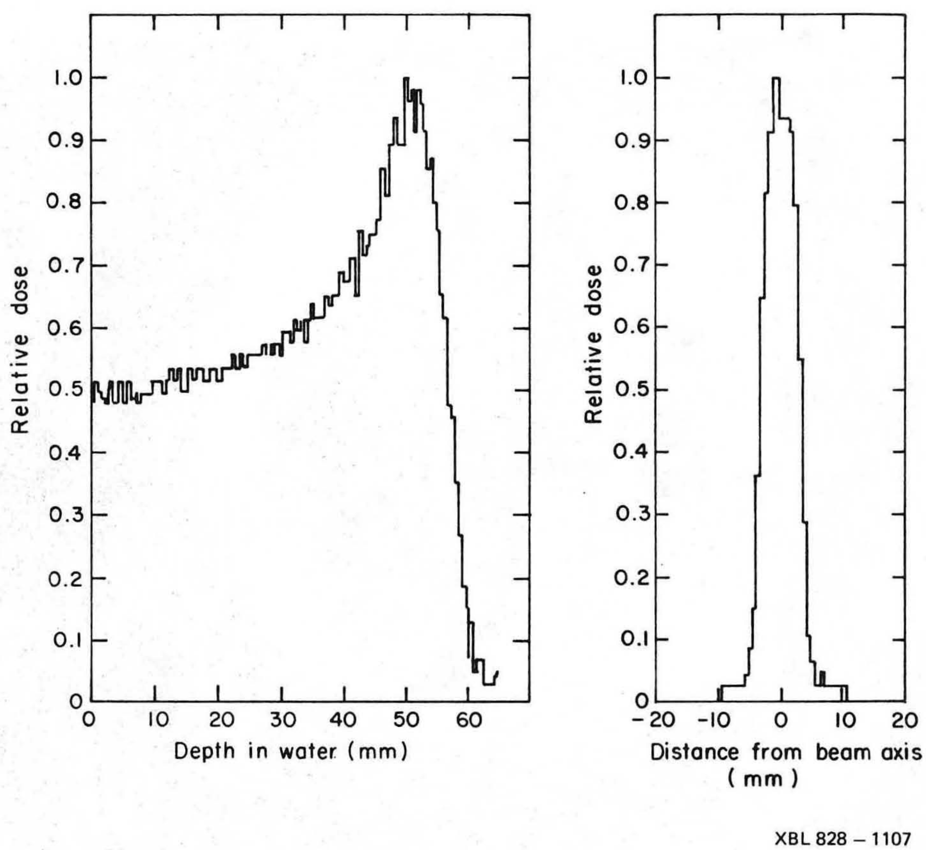
Figure 3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0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
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Depth in water (mm)
Relative dose
-20 -10 0 10 20
Distance from beam axis (mm)
XBL 828 – 1107

Figure 4

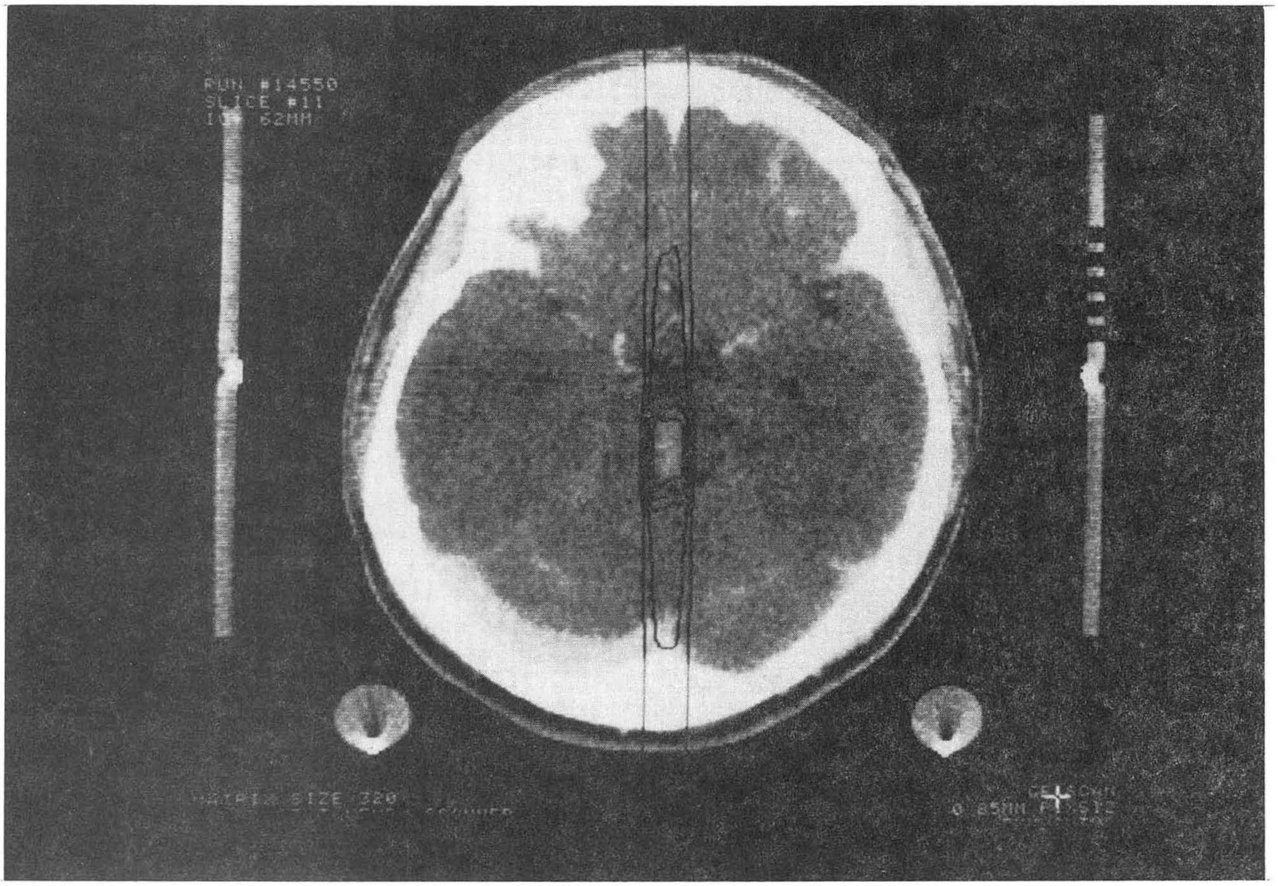

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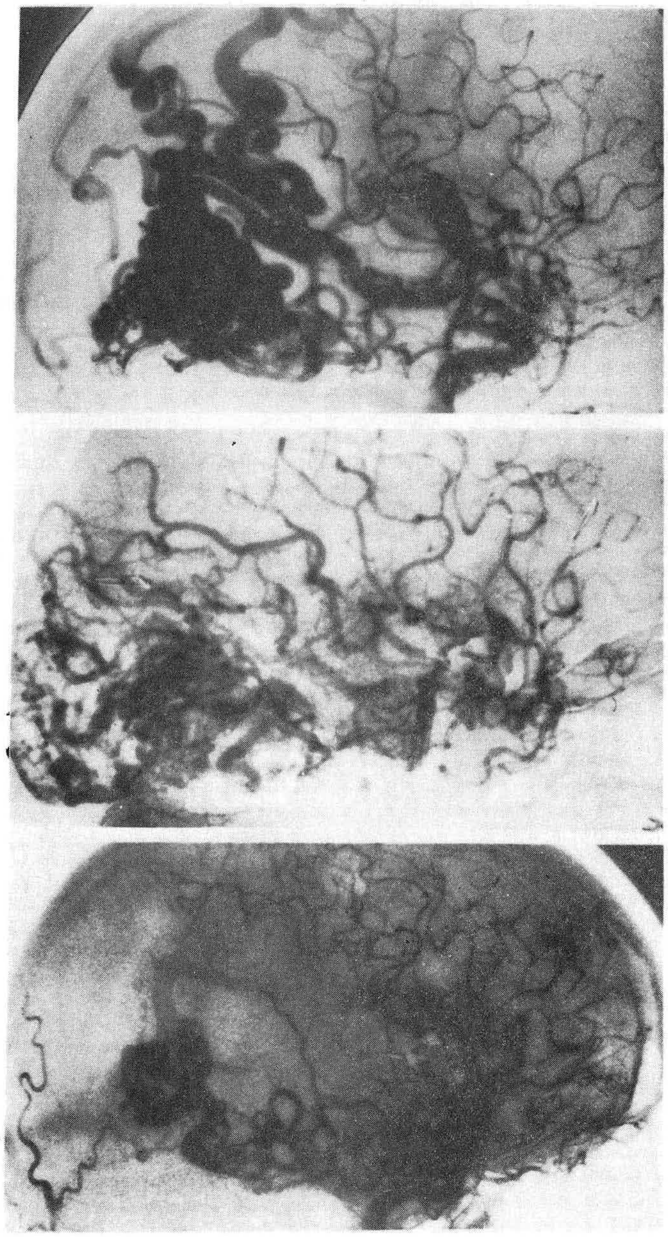
Figure 5



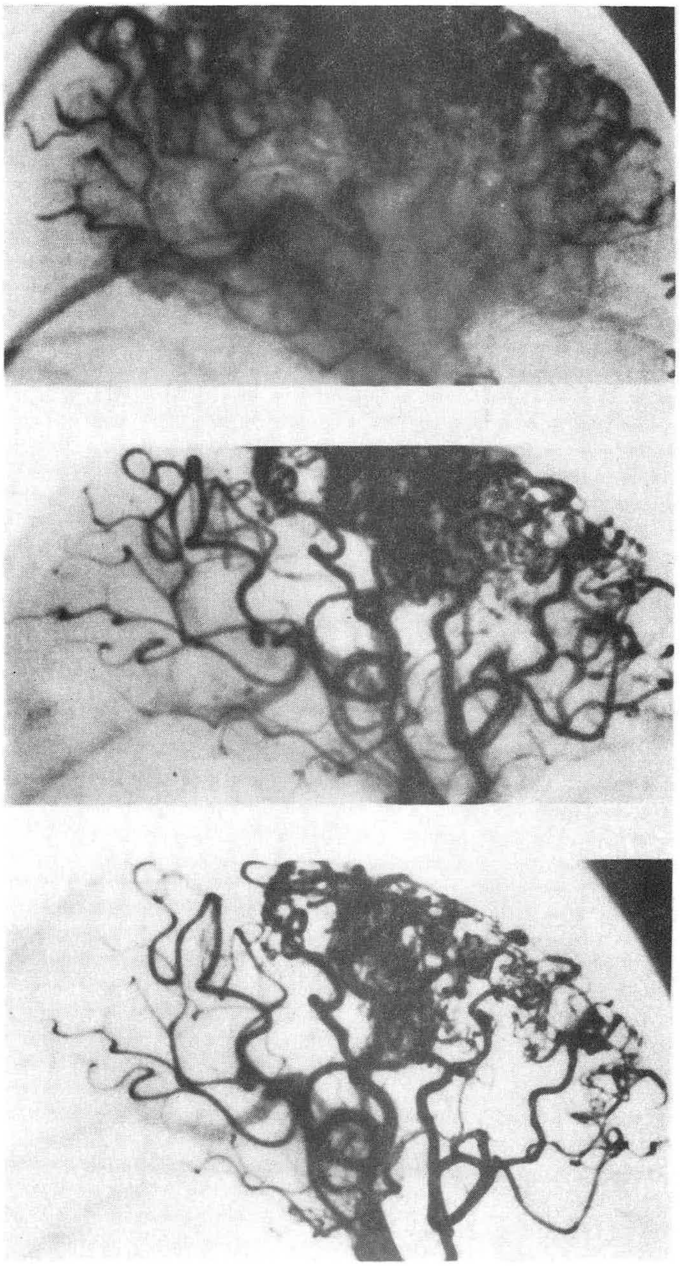
A

B

C

XBB 836-5168A

Figure 6



A

B

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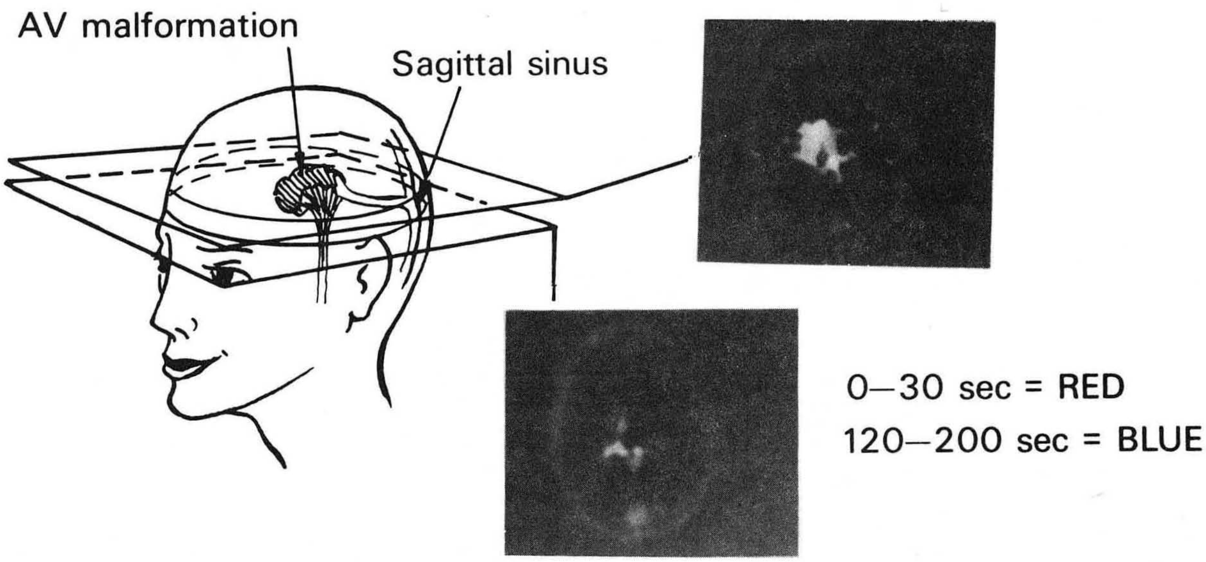
Figure 7



CBB 818-7343

Figure 8

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