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HEAVY PARTICLE IRRADIATION OF INTRACRANIAL LESIONS

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HEAVY PARTICLE IRRADIATION OF INTRACRANIAL LESIONS*

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INTRODUCTION

J. H. Lawrence, M.D.

Since 1935 there has been in this laboratory continuing interest in the investigation of the radio biology, the health hazards and the clinical therapeutic applications of the dense tissue ionization, produced by penetrating neutrons* and high energy penetrating charged particles, such as protons, helium nuclei and heavier particles, such as carbon and neon. Although our early studies led to the therapeutic use of neutrons in cancer therapy based on the apparent greater effect of neutrons on neoplastic tissue than normal tissue in mice (later explained by the so-called oxygen effect) and now being carried out at several other centers in the world (discussed in another chapter in the book); the present report will concern only positively charged particles.

Our first experience, beginning in the 1950's, involved the use of protrons and alpha particles to suppress the function of or ablate the pituitary gland in patients with breast cancer. Long-term results are

*J. H. Lawrence and E. O. Lawrence: THE BIOLOGICAL ACTION OF NEUTRON RAYS. Proc. Natl. Acad. of Sciences 22: 124-133, 1936.

J. H. Lawrence, P. C. Aebersold and E. O. Lawrence: COMPARATIVE EFFECTS OF X-RAYS AND NEUTRONS ON NORMAL AND TUMOR TISSUE. Proc. Natl. Acad. of Sciences 22: 543-557, 1936.

J. H. Lawrence, P. C. Aebersold and E. O. Lawrence: THE COMPARATIVE EFFECTS OF NEUTRONS AND X-RAYS ON NORMAL AND NEOPLASTIC TISSUE. American Assoc. Advancement of Science. Occasional Publications No. 4, pp. 215-219, June 1937.

in the area of the treatment of hypophyseal tumors, particularly hormone secreting tumors where we have had an experience extending over a period of more than 25 years.

We have organized this chapter into four sections: the first one, physical principles and techniques, by C. A. Tobias; the second, on our long-term experience with pituitary tumors; the third by Castro, et al., on neoplasms of the brain, spinal cord and eye; and the fourth section by Fabrikant et al., on the treatment of intracranial vascular disorders.

PART I

RADIOSURGERY WITH CHARGED PARTICLES: PHYSICAL PRINCIPLES AND TECHNIQUES

Cornelius A. Tobias

Introduction

William Bragg discovered in 1912 that alpha particles emitted from natural radioactive substances deposit in condensed matter more energy near the end of their ionization tracks than at the point of entry. The complete explanation of this property paved the way for important developments in nuclear physics. Thirty-four years later the Bragg ionization property became the basis of a suggestion by Robert Wilson (1946) that charged particles such as protons might be used in cancer therapy, where it is important to achieve good depth-dose localization of the ionizing particles.

In 1947, Ernest Lawrence completed construction of the first large synchrocyclotron at Berkeley, and for the first time beams of nuclear particles became available with sufficient range to penetrate deep-seated structures in the human body. In the same year, biomedical investigations were started with high energy protons, deuterons, and helium ions. In 1951, Tobias et al. demonstrated experimentally some of the physical properties of these particles and conducted initial biological experiments (Tobias et al., 1952). It became clear that the energetic light nuclei have excellent properties for producing clearly delineated lesions in mammalian tissues. Unlike electrons of electromagnetic radiations, which diffuse in tissues

because of strong scattering collisions, the nuclei propagated essentially along straight trajectories. It was this property that allowed careful aiming and, eventually, stereotactic localization of the irradiated regions.

The first use of proton beams on clinical patients was performed in 1955 with the goal of particle hypohysectomy to treat breast cancer metastatic lesions. Since that time there has been continuous progress in the methodology of applying particles for basic biomedical research, and clinical diagnosis and therapy (reviewed for example by Tobias, 1979). Beginning in 1971, atomic nuclei of carbon, neon, silicon, and argon became available for research studies at the Berkeley Bevalac (Ghiorso et al., 1973), and in 1982 the methods were extended to the acceleration of even the heaviest of the natural nuclei in the periodic table, uranium (Alonso et al., 1982). Proton irradiation is now being routinely administered at various centers: Harvard Unviersity (Suit and Goitien, 1980; Munzenrider, 1983), University of Uppsala (Larsson and Graffman, 1980), and at Moscow, Dubna, and Leningrad (Gol'din et et al., 1982) in the Soviet Union. The applications of heavy particles are too numerous to describe here, but most of them have been reviewed recently (Raju, 1980; Fowler, 1981; Pirruccello and Tobias, 1980). Plans are in progress in Canada, West Germany, and Japan to build heavy ion accelerators similar to the one in Berkeley, with the chief aim of applying heavy charged particles to basic biophysical research and to the diagnosis and therapy of cancer and other diseases.

Basic Physical Properties of Particle Beams

Accelerators usually produce highly monoenergetic and nearly parallel beams of particles. Essentially, these beams produce a straight pencil path in tissue, and essentially all particles stop at the same depth. However, the particles do deviate slightly from the straight line paths because of multiple elastic scattering, and their stopping points vary slightly because of a statistical variation in energy transfer called "straggling." Table I shows samples of theoretically achievable mean deflections and the magnitude of straggling in hydrogen, helium, and carbon beams.

The rate of energy transfer of particles to matter is a function of atomic number of the particles and of the particle energy. Typical Bragg curves from beams now in use at Berkeley are shown in Figure 1. The left side of this figure is the ionization curve of 225 MeV/n helium particles in water, which is nearly equivalent to soft tissue. This is the beam that has been used in our most extensive clinical study, pituitary irradiation, which has gone on for more than twenty years. The right side of Figure 1 shows the Bragg peak of a 308 MeV/n carbon beam from the Bevalac. This carbon beam has exquisite properties for heavy ion-radiography (Benton et al., 1973), and it is a candidate for future medical use in the production of highly localized lesions in brain and other body tissues. The heavy particle beams also produce secondary particles of lower atomic and mass numbers in a process of nuclear fragmentation. The dose from

fragmentation acts as a background, and it extends beyond the peak. For carbon, the relative magnitude of fragmentation dose is small, but this increases significantly for still heavier particles (Schimmerling, 1980; Llacer, 1983; Benton et al., 1983).

Classification of Particle Lesions

There are several simple methods of applying collimated particle beams to mammalian tissues.

Plateau lesions. A collimated beam, usually not more than a few millimeters in width, is allowed to pass through the head; the particles stop after they have crossed the head so that the plateau ions are used for irradiation. This method, sometimes called the "atomic knife," can produce sharply limited irradiated regions. With the aid of diagnostic X rays the beams can be focussed to any well-defined region; metal clips left in strategic locations by surgeons can also serve to guide the localization of the beam. A relatively small dose of a few hundred rad causes a transient increase in the permeability of the blood-brain barrier within the irradiated volume; there is no bleeding. At higher doses of possibly several thousand rad, local delayed radionecrosis occurs; the nerve tissue liquifies, glial reactions take place, and scar tissue develops. The scar tissue at the edge of the lesion usually occupies a narrower region than that which forms after surgically produced lesions. Perhaps the most interesting use of this technique so far has been the

cutting of the corpus callosum in cats using a knife edge beam of helium ions (Gaffey, 1973). This technique has been accomplished with no bleeding, and the thalamus, hypothalamus, pituitary, and brain stem were completely protected. When the lesion was wider than 0.4 cm, all neural communication between the two sides of the cerebrum ceased after an appropriate time interval.

Laminar lesions. Laminar lesions are radiolesions parallel to the surface of the brain. A strictly monoenergetic beam is passed into a specific area of the brain, possibly after a bone flap is removed. Because radiation effects in brain appear to have a threshold, it is possible to obtain lesions only at the Bragg peak. The sharpness of the Bragg peak in its relative height compared to the plateau region obviously relates to the minimal size of the lesions that can be achieved. The first such lesions have been obtained by Malis et al. (1957); Haymaker (1964) described many of the properties of such lesions. High energy carbon beams are probably best suited to deliver a minimal size of laminar lesion; the width of the lesion can be as small as 1/60 of the depth at which the lesion is made.

Focal lesions. Using a multiport irradiation technique, we may pass a number of shaped beams through the same small region of the body. In this manner we are able to produce small focal neurological lesions at any location in the head that has well-defined coordinates. This is the technique that has been used in the Berkeley series of pituitary irradiations for the treatment of acromegaly and

of Cushing's disease described in detail in this chapter. The pituitary gland, located at the geometrical center of the head, is a quite suitable target for such an approach.

The nominal dose given to the patient is the dose expressed in rad at the geometric center of the pituitary. The reason for quoting the nominal dose, which is also the maximum dose delivered to the center of the pituitary, is that it is convenient to measure: it is the sum total of beam doses passing through the external ion chamber integrator. Biologically, however, a more meaningful measure of dose is the rad dose at the peripheral edges of the pituitary. Numerically, the rad dose is about 50% of the nominal dose. The effectiveness of the rad dose given is further modified because of cellular repair between dose installments. The manner in which a variety of beams impinge on the pituitary over the course of therapy, and a three-dimensional dose distribution, is shown in Figure 2.

The isodose curves obtained with heavy charged particle are much better than the usual isodose curves one obtains with conventional radiation, which usually cannot avoid sensitive structures adjacent to the pituitary. A typical dose distribution used for an acromegalic patient treated at Berkeley is shown in Figure 3.

Histopathological observations from early pituitary patients who received helium therapy for metastatic mammary carcinoma confirmed that more than 95% of the pituitary cells can be eradicated and replaced with connective tissue after several months with nominal doses of 18,000 to 22,000 rad delivered over a 2 or 3 week period.

At lesser doses, it appeared that the magnitude of the histological effects depended on the dose at the periphery of the pituitary gland, where viable, hormone-secreting cells are found. Surviving cells from the lumen of the pituitary gland tend to migrate to the periphery where the blood supply is best.

The fractionated techniques used often complicate the evaluation of appropriate dose levels. Strandquist (1944) suggested that in a fractional irradiation scheme, the effective dose D can be expressed as: $D = d\ (T/t)^S$, where d is the dose in each fraction, T is the total number of treatments, and t is the number of days it takes to deliver the entire therapeutic sequence. The exponent s is determined empirically; it is always smaller than unity and it is a measure of repair occurring between dose installments. For skin, Strandquist found s = 0.22, whereas DuSault later determined s = 0.27 (1962). For rabbit and for human brain tissue, where large volumes of the brain were exposed to X rays in a total of 17 patients, Ludgren used s = 0.27.

Figure 4 is a Strandquist plot of some of the actual dose schemes we used to treat diabetes and mammary cancer. The center of the pituitary gland received fractionated doses that were equivalent in effect to a single dose of 4,500 to 6,500 rad (diabetes) or 8,000 to 18,000 rad (mammary cancer). The local doses considered without demonstrable effects to the temporal lobe are 1,500 rad in 12 days, corresponding to 800 rad single doses for patients with diabetes and vascular disease, and 2,000 rad in 12 days, or about 1,100 rad single

dose for other patients who have normal vascular structures. These local temporal lobe doses can be calculated for a distance of 2.1 cm from the center of the pituitary. This is the point at which a temporal lobe dose is at its highest; the dose falls very rapidly with distance from the pituitary.

Focal Bragg peak lesions. Further depth-dose improvements are reached in focal irradiation if the Bragg peak of the beams are allowed to stop in or near the focal region. Figure 5 shows the great improvement in dose distributions one may reach by using the focal Bragg peak technique. This approach has been used for some of the acromegaly irradiations at Harvard and at Berkeley; however, the proper use of this technique involves the exact knowledge of the stopping power of intervening tissues. For proton and helium beams, this is done on the basis of X-ray tomography and calculations based on stopping power measurements of the beam passed through the head. These techniques need further improvement: The quantitative information on electron densities that one can obtain from X-ray tomography has possible errors because of X-ray hardness artefacts and because the X-ray techniques usually measure attenuation coefficients instead of electronic stopping power. There are also limitations in the ordinary focal pituitary irradiation; the dose delivered to the cranial nerves and to the temporal lobes are limiting. Furthermore, because of beam scattering, sometimes the ocular nerves and chiasm, lying only a few millimeters from the sella turcica, may get more irradiation than desired.

The heavier ion beams, particularly carbon and neon, promise to be much more suitable for the delivery of focal Bragg peak irradiations, not only because of reduced scatter and the sharpness of their Bragg peaks, but also because it is possible to obtain beams of some of their radioactive isotopes (Chatterjee et al., 1981). When a carbon beam is passed through an absorber of modest thickness, some of the carbon-12 particles change into radioactive carbon-11. The carbon-11 particles can be collected in a beam separate from the parent carbon-12 beam. If irradiation is performed using carbon-11, then the particles first come to a stop in tissue and later decay with a half-like of 21.5 minutes. Using a special gamma-ray camera one may locate the stopping point of the beam with an accuracy of about 0.1 cm while the irradiation is still in progress. For neon, the Ne-19 isotope is used, which has a half-life of a few seconds. The data obtained from the gamma-ray camera allow a continuous check on the correctness of the depth of the stopping point of the beam while the radiation is administered, and should lead to greatly increased accuracy in the delivery of stereotactic microfocal irradiation. Figure 6 is an artist's view of the way focal Bragg peak radiation might be administered in the future. A special gamma-ray camera has already been built for the purpose of imaging the location of radioactive beam particles in the body. We expect that within a few years the use of radioactive beams will become the treatment of choice in microfocal particle irradiations. It will be then possible to deliver greater doses to smaller structures in the brain than is

feasible with protons or with helium, and the adjacent tissues will be better protected from radiation effects than at present.

Localized Tumor Therapy

There is a substantial effort under way at Berkeley to use accelerated heavy ions for localized therapy of tumors. A complex rationale has been developed based on the biological effectiveness of the particles, on their ability to reduce the radiobiological oxygen effect, and on the extent of intracellular repair and sensitivity changes during the cell division cycle (Tobias et al., 1982). A special computerized approach has been created for therapy planning (Chen and Pitluck, 1983), which takes into account a variety of diagnostic information, including computerized axial tomography. The depth penetration properties of the particles are also used in the therapy plan. A detailed study of heavy ion radiobiology indicates that silicon or argon ions might be more effective than lighter ions for localized cancer therapy.

REFERENCES

Alonso, J. R., R. T. Avery, T. Elioff, R. J. Force, H. A. Grunder, H. D. Lancaster E. F. Lofgren, J. R. Meneghetti, P. B. Selph, R. R. Stevenson, and R. B. Yourd. (1982). Acceleration of uranium at the Bevalac. Science 217, 1135-1137.

Benton, E. V., R. P. Henke, and C. A. Tobias, (1973). Heavy particle radiography. Science 1982, 474-486.

Benton, E. V., C. A. Tobias, and E. A. Blakely. (1983). Heavy ion fragmentation studies with plastic nuclear detectors. Radiat. Res., in press. (Abstract.)

Chatterjee, A., E. L. Alpen, J. Llacer, J. R. Alonso, and C. A. Tobias. (1981). High energy beams of radioactive nuclei and their biomedical applications. Int. J. Radiat. Oncol. Biol. Phys 7, 503-507.

Chen, G.T.Y, and S. Pitluck (1983). Treatment planning for heavy charged particle radiotherapy. Pion and Heavy Ion Radiotherapy: Pre-Clinical and Clinical Studies (L.D. Skarsgard, ed.), pp. 149-158. Elsevier Biomedical, New York/Amsterdam.

DuSault, L. A. (1962). The influence of the time factor on the dose-response curve. Am. J. Roentgen. 87, 567.

Fowler, J. R. (1981). Nuclear Particles in Cancer Treatment. Adam Helger Ltd., Bristol, England.

Gaffey, C. T. (1973). Split beam cats prepared by radiosurgery. Int. J. Radiat. Biol. 24, 229-242.

Ghiorso, A., H. A. Grunder, W. Hartsough, G. Lambertson, E. Lofgren, K. Lou, R. Main, R. Mobley, R. Morgada, W. Salsig, and F. Selph. (1973). The Bevalac: An economical facility for very high energetic heavy particle research. IEEE Trans. Nucl. Sci. NS-20, 155 (Abstract).

Gol'din, L. L., I. V. Chuvilo, and A. I. Ruderman. (1982). Application of Charged Heavy Particles in Medicine. Joint Institute for Nuclear Research, Report JINR P 18-82-117. Dubna, U.S.S.R.

Haymaker, T. (1964). In Response of the Nervous System to Ionizing Radiation (T. J. Haley and R. S. Snider, eds.). Little Brown and Co., Boston.

Kjellberg, R. N. and B. Kleman (1979). Lifetime effectiveness--A system of therapy for pituitary adenomas emphasizing Bragg peak proton hypophysectomy. Recent Advances in the Diagnosis and Treatment of Pituitary Tumors (J. A. Linfoot, ed.), pp. 269-288. Raven Press, New York.

Larsson, B. and S. Graffman (1980). Proton beams in biomedical research: Experience and plans in Uppsala. Maria Design Symposium. Vol. II: Radiation Oncology Workshop. Medical Accelerator Research in Alberta, Edmonton, Alberta Canada.

Llacer, J. (1983). Characterization of fragments in heavy ion beams with a simple semi-conduction telescope. Radiat. Res., in press (Abstract).

Malis, L. I., R. Loevinger, and J. E. Rose. (1957). Production of laminar lesions in the cerebral cortex by heavy, ionizing particles. Science 126, 302-303.

Munzenrider, J. E. (1983). Proton therapy at Harvard. Pion and Heavy Ion Radiotherapy: Pre-Clinical and Clinical Studies (L. D. Skarsgard, ed.), pp. 363-372. Elsevier Biomedical, New York/Amsterdam.

Pirruccello, M. C. and C. A. Tobias, eds. (1980). Biological and Medical Research with Accelerated Heavy Ions at the Bevalac, 1977-1980. Lawrence Berkeley Laboratory Report LBL-11220.

Raju, M. R. (1980). Heavy Particle Radiotherapy. Academic Press, New York.

Schimmerling, W. (1980). Experimental heavy particle physics. A. Nuclear interactions and radiation dosimetry. Biological and Medical Research with Accelerated Heavy Ions at the Bevalac, 1977-1980 (M. C. Pirruccello and C. A. Tobias, eds.), pp. 35-41. Lawrence Berkeley Laboratory Report LBL-11220.

Strandquist, M. (1944). Studien uber die Kumulative Wirkung der Rontgenstrahlen bei Fraktionierung. Acta Radiol., Supplement 55.

Suit, H. D. and M. Goitein. (1980). In Radiation Biology and Cancer Research (R. Meyn and R. Withers, eds.), pp. 195-230. Raven Press, New York.

Tobias, C. A. (1979). Pituitary radiation: Radiation physics and biology. Recent Advances in the Diagnosis and Treatment of Pituitary Tumors (J. A. Linfoot, ed.), pp. 221-243. Raven Press, New York.

Tobias, C. A., H. O. Anger, and J. H. Lawrence. (1952). Radiological use of high energy deuterons and alpha particles. Am. J. Roentgenol., Radium Ther, Nucl. Med. 67, 1-27.

Tobias, C. A., E. A. Blakely, E. L. Alpen, J. R. Castro, E. J. Ainsworth, S. B. Curtis, F. Q. H. Ngo, A. Rodriguez, R. Roots, T. S. Tenforde, and T. C. Yang. (1982). Molecular and cellular radiobiology of heavy ions. Int. J. Radat. Oncol. Biol. Phys. 8, 2109-2120.

Wilson, R. R., Radiological use of fast protons. (1946). Radiology 47, 487-491.

Table I. Scattering: Particles of 14-cm range in water.

	Mean Lateral Deflection (cm)	Mean Straggling (cm)
Hydrogen	0.4	0.14
Helium	0.2	0.09
Carbon	0.12	0.04

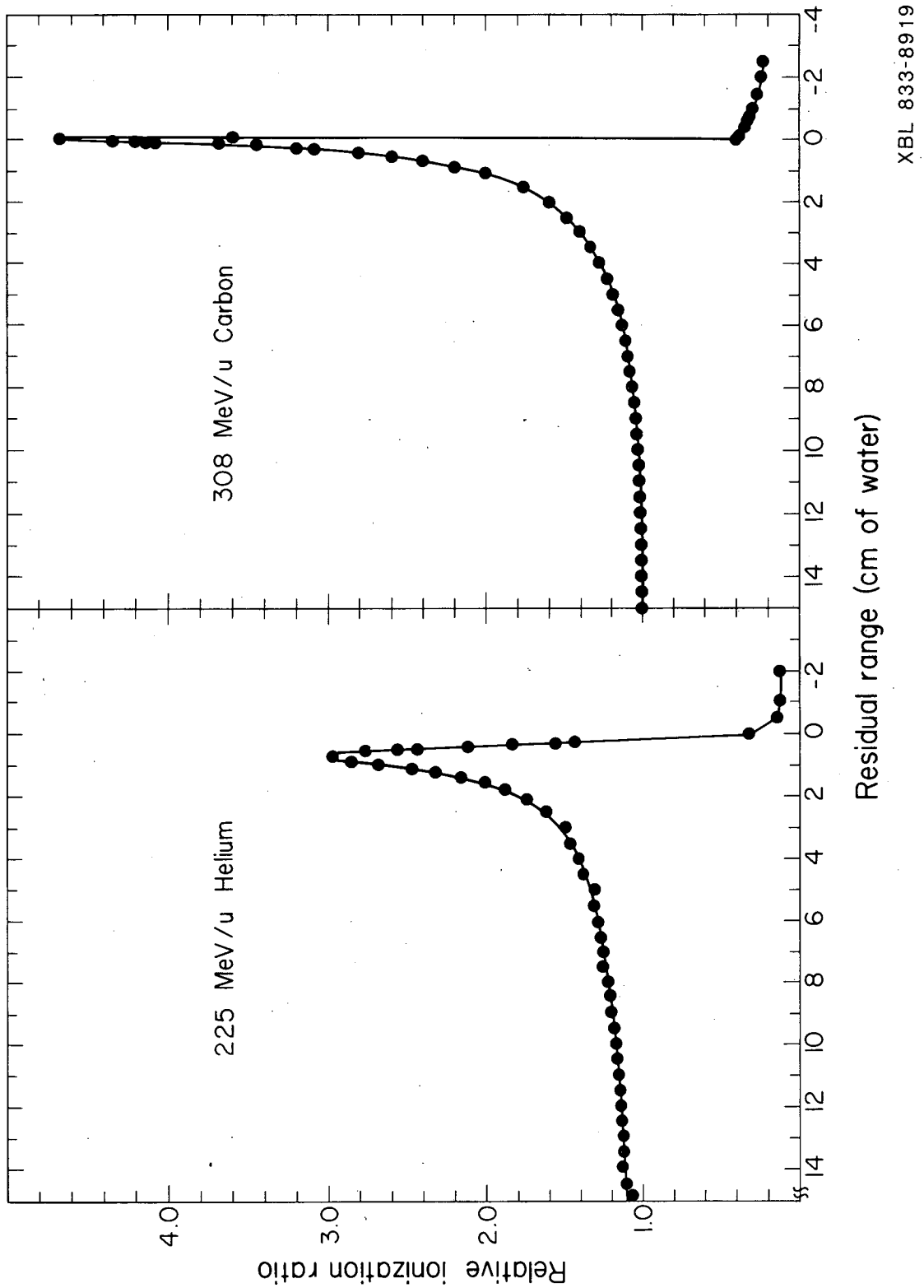

225 MeV/u Helium
308 MeV/u Carbon
Relative ionization ratio
1.0
2.0
3.0
4.0
Residual range (cm of water)
-4
-2
0
2
4
6
8
10
12
14
XBL 833-8919

Fig. 1

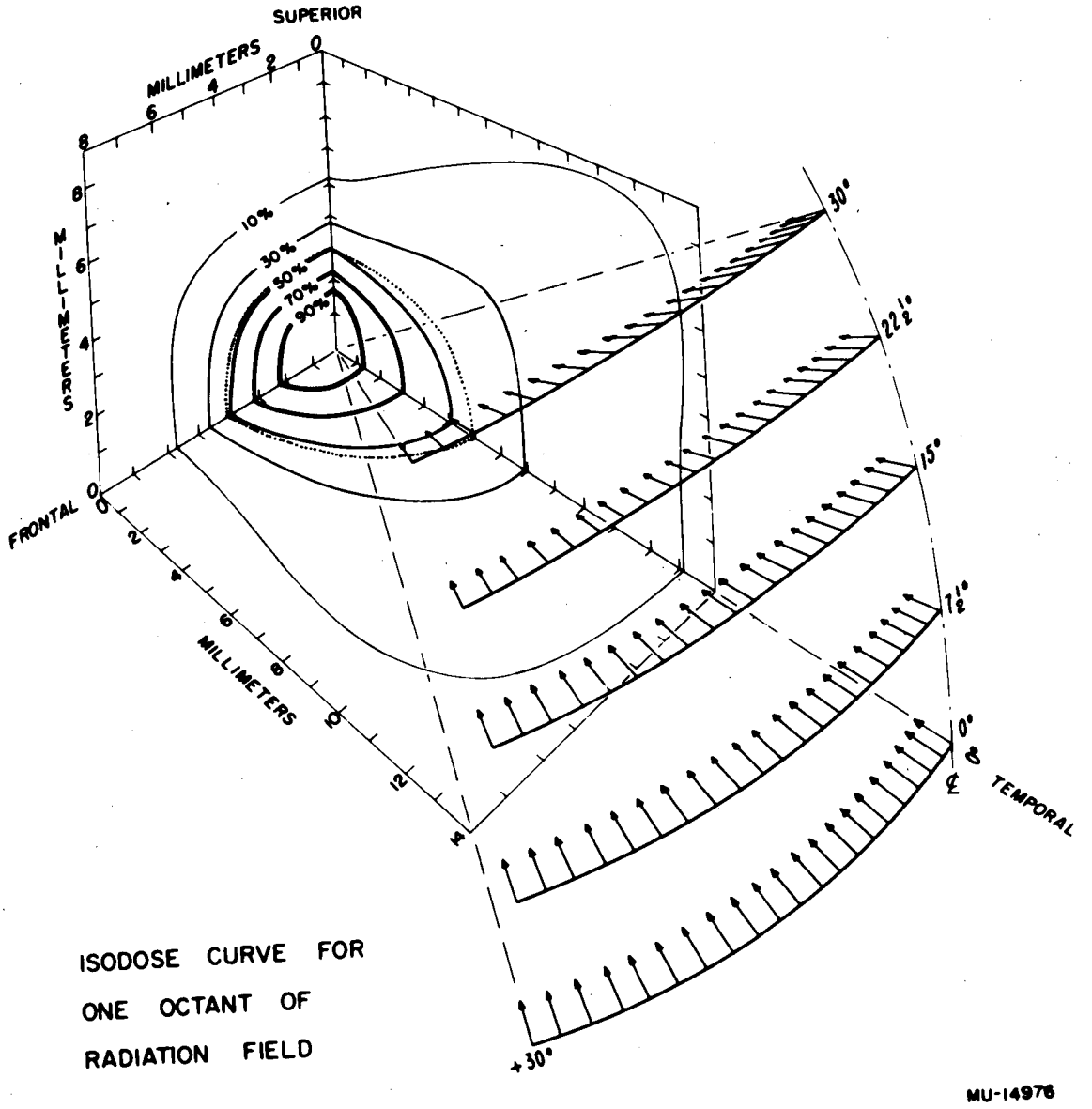
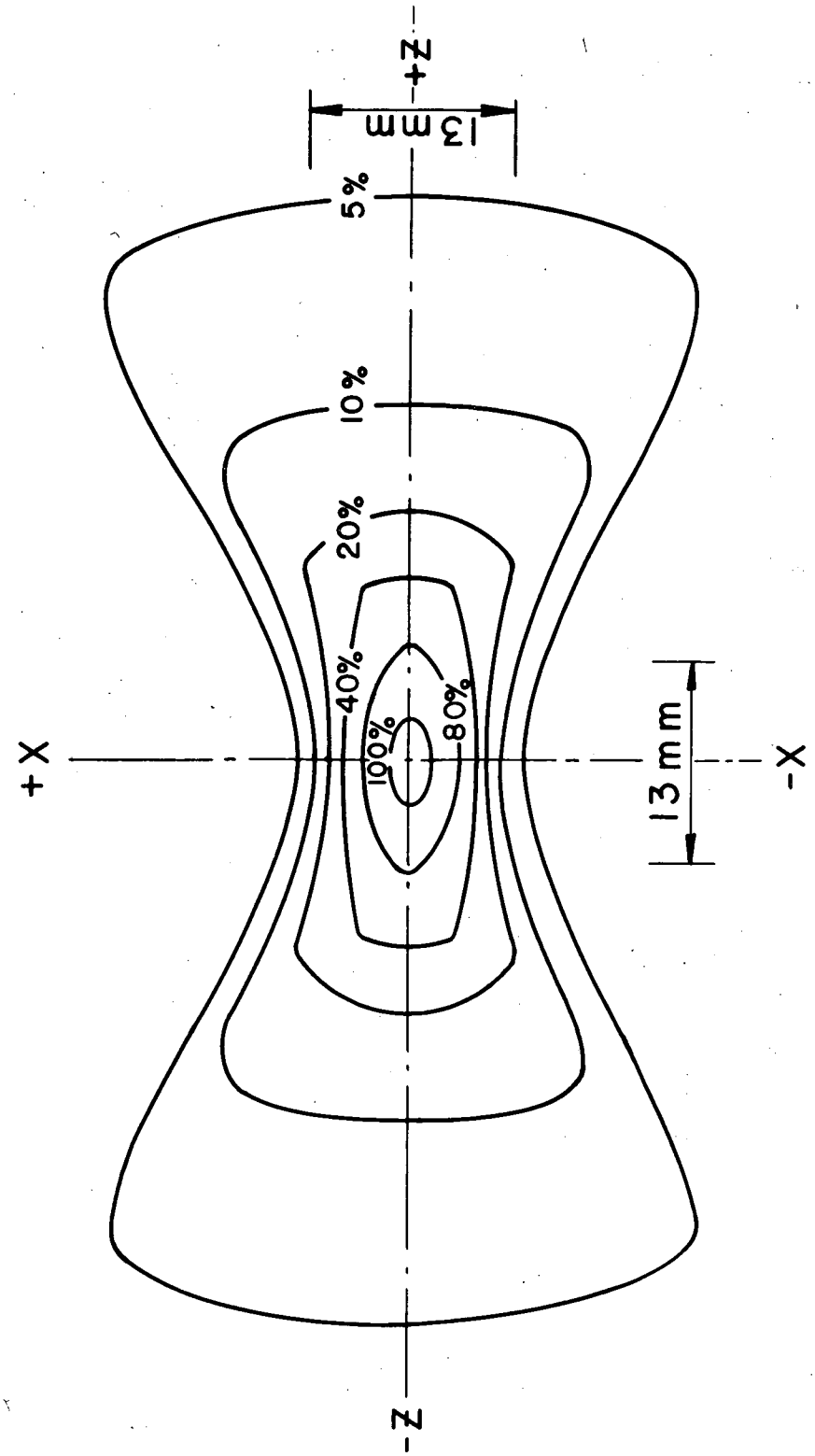

SUPERIOR
MILLIMETERS
0
2
4
6
8
MILLIMETERS
10%
30%
50%
70%
90%
FRONTAL
MILLIMETERS
30°
22½°
15°
7½°
0°
TEMPORAL
+30°
ISODOSE CURVE FOR
ONE OCTANT OF
RADIATION FIELD
MU-14976

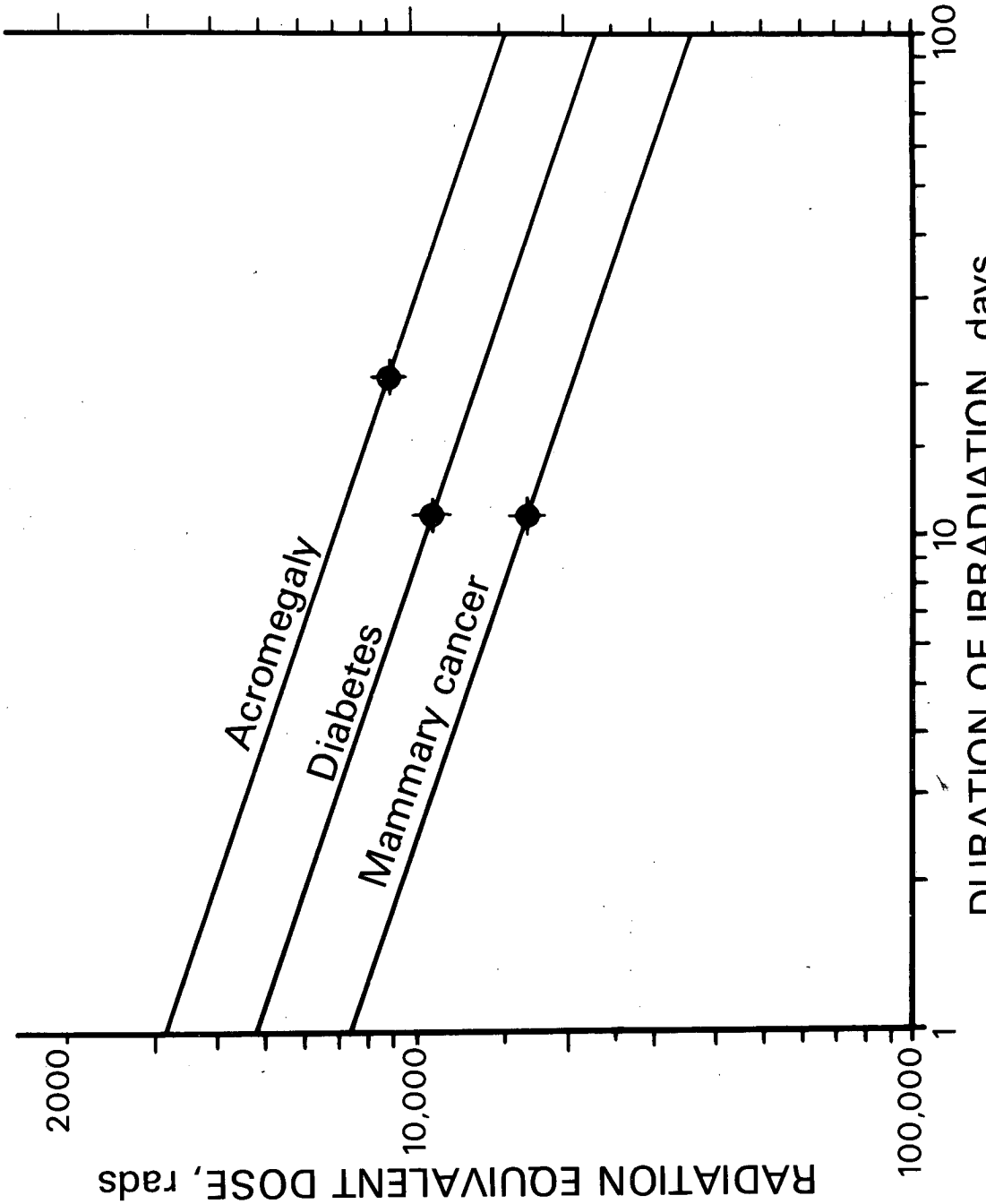
Fig. 2



ISODOSE CURVE - LATERAL PLANE

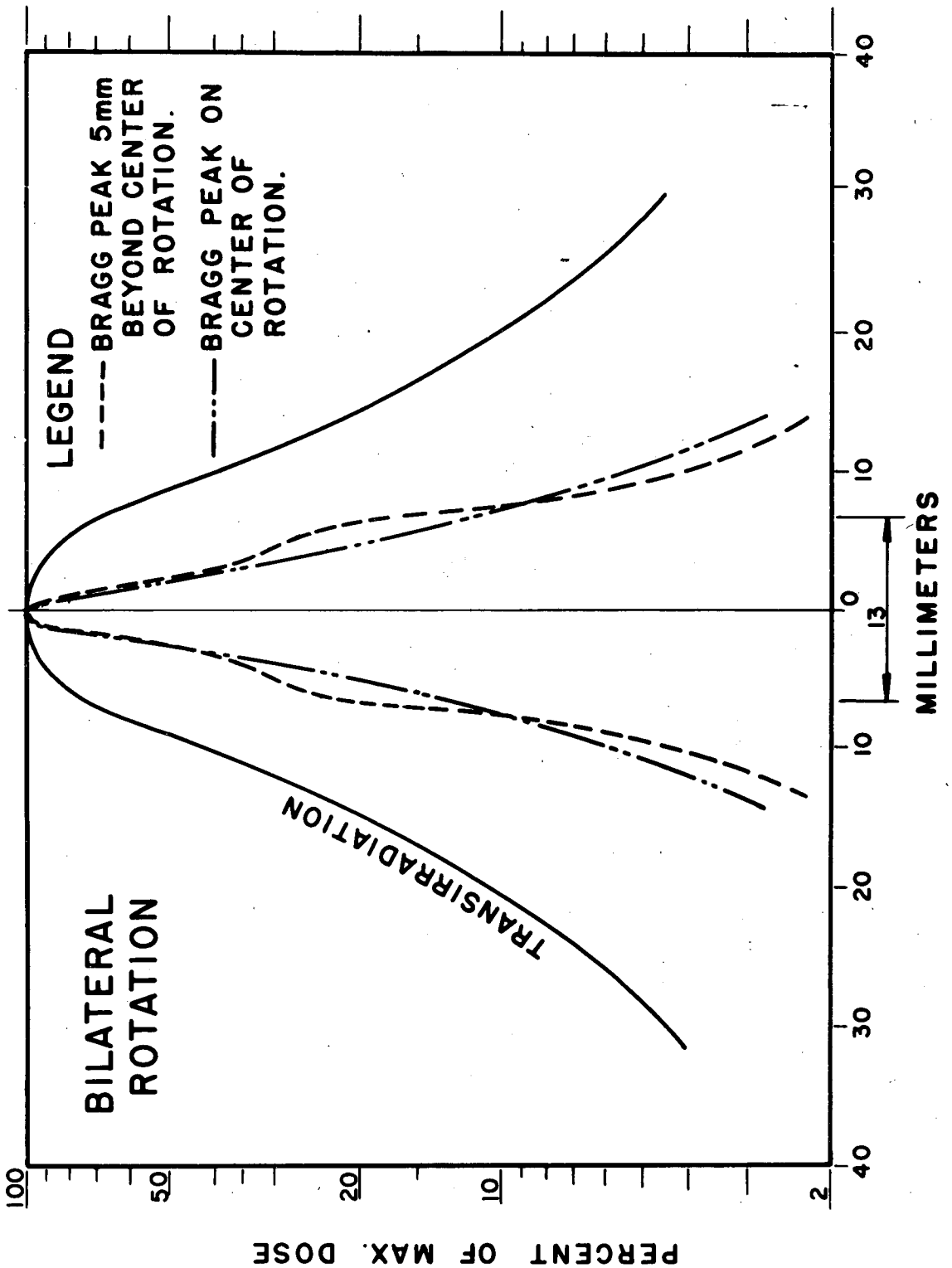
XBL 785-8713

Fig. 3



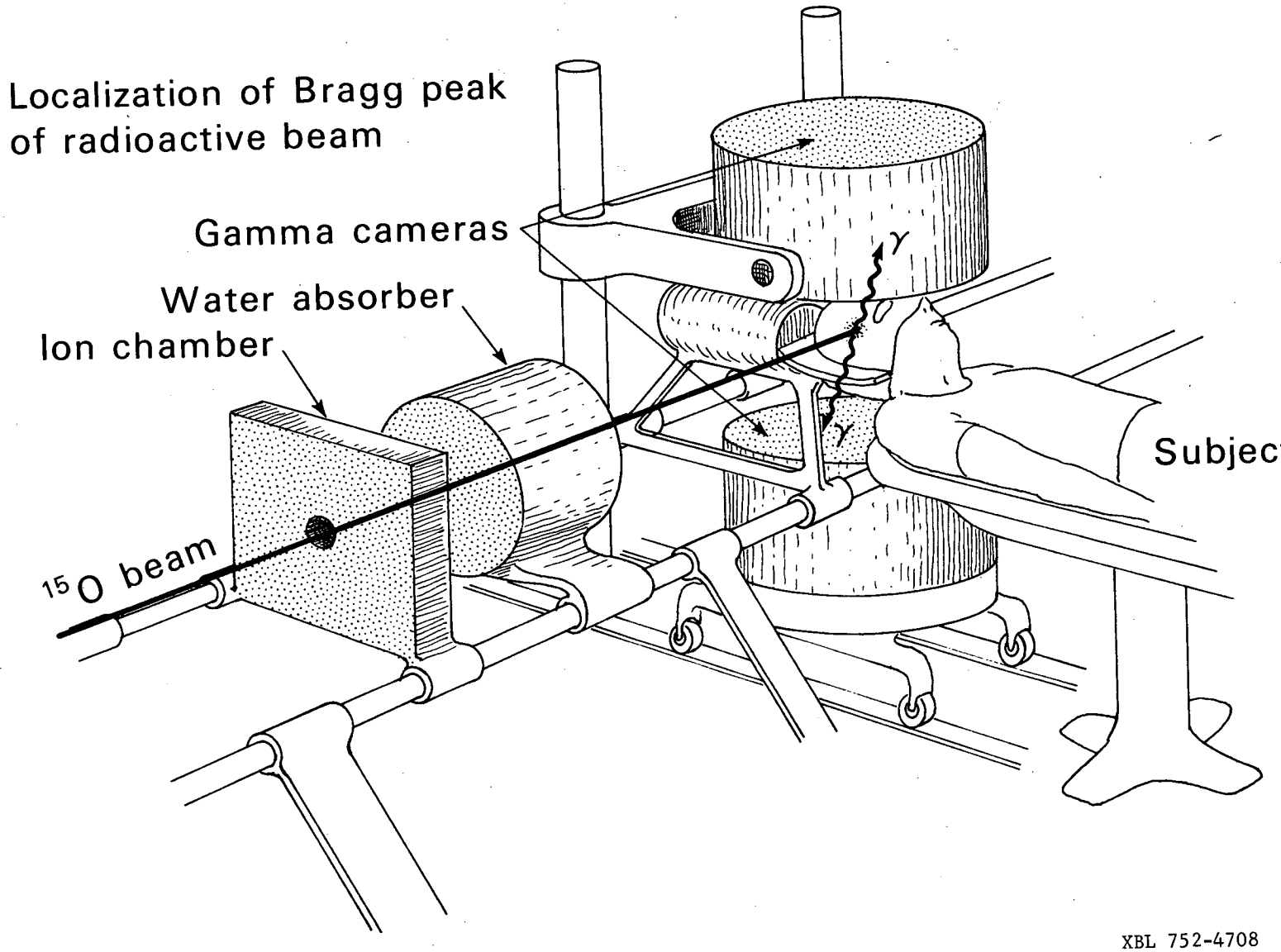
XBL 785-8697

Fig. 4



XBL 785-8710

Fig. 5



XBL 752-4708

Fig. 6

PART II

THE ROLE OF HIGH ENERGY PARTICLE THERAPY IN THE TREATMENT OF FUNCTIONING PITUITARY TUMORS

J. A. Linfoot, M.D.* and J. H. Lawrence, M.D.

Introduction

Our first experience, beginning in 1957, involved the use of protons and alpha particles to suppress the function of or ablate the pituitary gland in the therapy of hypophyseal tumors, particularly hormone secreting tumors. This work has been reported over the years in considerable detail, metabolic and clinical, on a large series of patients with acromegaly.

A recent compendium (1) discussed, by a wide spectrum of experts, the many advances in the diagnosis and treatment of various hypophyseal tumors. Treatment modalities discussed included surgery (transsphenoidal and transfrontal), heavy particle irradiation (2) and conventional irradiation (X-rays or gamma rays), the implantation of radioactive seeds, cryosurgery and thermocautery.

Since 1957 alpha particles (helim ions) have been used to suppress pituitary function in 807 patients with a variety of neoplastic and metabolic disorders including mammary carcinoma (3), diabetes complicated by retinopathy, and functioning and nonfunctioning pituitary tumors (4,5,6,7). This review presents our experience in the treatment of 314 acromegalic patients, macro- and

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microadenomas, using alpha particle pituitary irradiation (APPI). The duration of follow-up in these patients ranges from 4 to greater than 20 years, with the majority of patients having been followed for 10 years or more.

Radiotherapeutic Technique

A system for pituitary irradiation was developed using a projected (3) physical dose system with a geometric delivery that limits the volume of extrasellar tissue irradiated by the particle beam. A pencil-shaped beam is shaped to fit the contour of the sella turcica, and with multiport exposure and with a sequential pendulum motion, a dose distribution is achieved that maximizes the particle beam at the center of the pituitary while protecting the basal structures, e.g., the optic chiasm, brainstem, and hypothalamus. In most of the patients the beam is passed through the head and referred to as the plateau or "through-and-through" technique. The use of the Bragg peak to selected patients with large tumors was limited, although this method has been used extensively by other investigators (8). Therapy is fractionated and administered in four treatments over 4- to 5-day period. The patients are individually fitted with bivalved head holders which ensure that the head is rigidly fixed to the adjustable treatment table, permitting no more than 1 mm of movement within the head holder. A brass collimating aperture is selected and fitted to the size and configuration of the tumor. With the aid of diagnostic X-rays, desired alignment is achieved and the treatment plan is programmed on a computer. The specially designed treatment table

allows the head and trunk to be independently rotated during therapy. The high-energy particles have sufficient energy to penetrate the entire thickness of the skull. The skin dose and the dose to the peripheral portions of the brain are minimal, and no epilation occurs. The optic chiasm, hypothalamus temporal lobes and outer portions of the sphenoid sinus receive less than 10% of the central pituitary dose.

Patient Selection Criteria

Criteria for the selection of patients for alpha particle pituitary irradiation included:

a) confirmed presence of a pituitary tumor by neuroradiological or histological examination;

b) demonstrated pituitary hypersecretion with detectable endocrine or metabolic effects;

c) absent history of prior therapeutic irradiation to the pituitary or parasellar structures;

d) absence of major suprasellar extension;

e) cerebrospinal fluid (CSF) growth hormone level <1.5 ng/ml (9) in patients with pituitary gigantism or acromegaly;

f) pituitary size <2.5 cm;

g) clearly definable radiological tumor landmarks in the presence of extensive sphenoid extension;

h) adequate localization of the optic chiasm and residual tumor mass in post-surgical patients.

Using these criteria, pituitary tumor therapy has been achieved with a high degree of success and low morbidity.

The invasive grade III and IV tumors were common in the series and were usually associated with marked extension into the sphenoid as well as indeterminate lateral extension into the cavernous sinus.

Goals of Treatment

Four primary goals with APPI are:

a) control of tumor growth;

b) control of hormonal hypersecretion;

c) acceptable hormonal side effects;

d) no central nervous system (CNS) side effects.

ARPI has been suitable as a primary treatment in the majority of referred patients. In recent years many patients have been referred following transfrontal or transsphenoidal surgery because of recurrence or partial or incomplete surgical tumor removal, thus permitting a comparison of the more recent combined therapy and the prior experience with de novo treatment. Combined therapy is desirable in many patients with invasive tumors. Inability to appreciate early invation of the dura, multiple microadenomas or adenomatous hyperplasia (10,11) are causes of treatment failure with transsphenoidal hypophysectomy. In the case of large tumors, the inability to visualize and excise pockets of invasive tumor, resulting in inadequate control of hormonal hypersecretion and successful control of tumor regrowth, is a therapeutic limitation for all

surgical approaches. Mass control is achieved with conventional radiotherapy but control of hormonal hypersecretion is often limited (12).

Acromegaly

A total of 314 patients with acromegaly were treated with APPI. The analyses are based upon those patients having pre- and post growth hormone studies (299 pts). Figure 1 shows the fall in the average fasting growth hormone performed on two or three consecutive mornings of patients treated with APPI. The decrease in plasma growth hormone has been associated with striking clinical and metabolic improvement (e.g., improved glucose tolerance, loss of insulin resistance, and fall in elevated serum phosphorus levels) and is frequently seen within the first year even before the growth hormone levels fall to 10 ng/ml. The rate of fall of patients treated surgically prior to APPI was slower but paralleled that of the de novo group. Growth hormone levels fell to 5 ng/ml in 30% of the patients within 2 years, 68% within 6 years, and 95% within 8 years.

In order to evaluate the influence of tumor size, the acromegalic patients were categorized into four groups according to sellar volume. Patients in group I had microadenomas; group II included patients with grades II through IV tumors. In spite of progressively increasing mean growth hormone levels with increasing sella size, there was a great deal of overlap in groups II and IV.

Microadenoma patients responded extremely well. Invasive tumors (grades III and IV) present difficult therapeutic geometry for heavy

particle therapy and have a less favorable prognosis. Similar findings have been seen in transsphenoidal patients (13). Combined use of surgery and APPI is probably the optimal therapy in these difficult cases.

Relapse in Acromegalic Treatment

Relapses or failures are considered to be those patients who have failed to show clinical improvement or return of growth hormone levels to 10 nanograms per millimeter or less. Less than 10% of patients treated with helium nuclei as primary treatment have required subsequent surgery (Figs. 2 and 3).

Recently, transsphenoidal microsurgery has been employed by a large number of neurosurgeons with impressive success, Charles Wilson, being a leader in this work (13,14,15,16). In Boston, Kjellberg et al. (17) and in Russia, Ruderman et al. (18) have been using protons in the therapy of pituitary tumors. Centers in France, Canada, Great Britain, Germany, Japan, Sweden, and the United States are planning to use or see currently using pi-mesons or well-collimated photons for intracranial tumors. However, it will be several years before the results of these methods, in a large enough series with long follow-up, be it surgery or irradiation, can be compared or analyzed with the series reported here.

Relapse in alpha particle therapy was usually the result of failure to appreciate the presence of some degree of extrasellar extension. Through retrospective analysis four major reasons for what is referred to as "geometric misses" have been identified:

a) Failure to appreciate a small suprasellar extension was relatively uncommon in recent years when hypocycloidal polytomography during pneumoencephalography (PEG) was employed and have complemented PEGs with the use of CSF growth hormone measurements (9) to confirm the presence or absence of suprasellar extension in equivocal examinations. New generation CT scans with thin section sagittal, coronal, and axial reconstruction have replaced PEGs.

b) Intrasphenoidal extension accounts for 50% of the relapses.

c) Posterior inferior extension into the region of the clivus was a less common site for unsuspected tumor extension.

d) Prior to the advent of new generation CT scans, lateral extension into the cavernous sinus was difficult to detect in the majority of cases.

Encocrine Effects in Acromegaly

A total of 233 patients were analyzed who had received APPI as sole or de novo treatment, and 65 patients received APPI following surgical hypophysectomy. Adrenal replacement data are shown in Table 1: 150 (65%) of the de novo patients treated only with APPI are currently on no adrenal replacement; 3 patients (1%) were on adrenal steroids prior to treatment; and 80 patients (34%) have been placed on adrenal steroids after irradiation. Twenty-nine percent of patients who had surgery prior to APPI are on no adrenal replacement; 39% were on replacement prior to APPI; and 34% required replacement after APPI.

Similar data were observed for thyroid replacement (Table 5): 61% of the de novo patients are on no thyroid replacement; 6% were on thyroid prior to APPI; and 33% are on thyroid after APPI. In the surgical group 20 patients (31%) are on no replacement; 27 patients (41%) were on thyroid after surgery; and 18 patients (28%) were given thyroid after the combined treatments.

Gonadal steroid replacement (Table 3) with estrogen or testosterone is perhaps somewhat less reliable as an estimate of gonadotropin deficiency since many of the older patients may not be given gonadal steroids in spite of some degree of hypogonadism. Seventy-three percent are on no gonadal steroid replacement; 2% were on gonadal steroids before treatment; and 25% are on replacement after APPI. Forty-nine percent of the patients who had prior surgery, are on no replacement; 22% were on gonadal steroids prior to APPI; and 29% are on replacement after combined treatment.

Identification of the location of the extrasellar extension in patients who had "geometric misses" has assisted transsphenoidal microsurgery. Patients with persistent tumor activity have been successfully managed by either transsphenoidal hypophysectomy or transcranial subfrontal hypophysectomy followed by APPI, complete normalization of growth hormone was achieved in this group of patients with invasive tumors.

Complications of Alpha Particle Therapy in Acromegaly

Complications other than endocrine complications have been largely limited to those patients who received previous unsuccessful photon

therapy; 29% had partial field cuts which fortunately did not impair visual acuity and are asymptomatic. Three patients (43%) developed unilateral extraocular motor nerve (usually third nerve) lesions, which usually cleared and were relatively asymptomatic. Three of these patients developed temporal lobe epilepsy due to focal radiation necrosis of the temporal lobes; this was easily controlled with anticonvulsant therapy. As a result of these early complications patients who had received prior photon therapy have not been accepted for treatment since 1961.

A second group of patients with complications are those who were initially treated with Bragg peak therapy. Thirteen percent developed small field cuts immediately following treatment which subsequently cleared. Two patients (25%) had transient unilateral third nerve lesions which cleared, and one (13%) of these patients developed temporal lobe epilepsy that is controlled by anticonvulsant medication.

Of the 308 patients who received the "through and through" technique, only two patients treated prior to 1961 received higher doses of radiation than is currently used and both developed temporal lobe symptoms. The overall incidence of CNS complications (298 acromegalic patients) is 4%. This complication rate is less than described for photon therapy which, on the basis of recent data, employs lower total doses and lower doses per fraction than were employed several years ago (19,20).

Survival is compared with an age-sex matched set of diabetic patients treated with alpha particle irradiation and an age-sex matched set of the general population. Figures 2 and 3 show the increasing survival with the passage of time. Most of the patients are still alive, hence per cent survival will increase with the passage of time. There have been 48 deaths in our acromegalic series, the major cause being cardiovascular disease (Table 4). The life expectancy of the acromegalic patients has been improved with APPI, which is free of operative morbidity, and has had minimal CNS morbidity and a significant but acceptable incidence of hypopituitarism. (Tables 1, 2 and 3).

In the primary treatment of acromegaly, grade I and grade II cases appear to do as well as patients who have had surgical transsphenoidal hypophysectomy. The response following APPI is delayead, although more rapid than that seen following photon therapy. The incidence of hypopituitarism is greater than after transsphenoidal hypophysectomy and probably less than photon therapy because of the lack of any hypothalamic irradiation with APPI. The response to treatment in grade II and IV lesions are further delayed, but ultimate normalization of growth hormone as well as tumor control can be achieved if the extent of tumor invasion is fully appreciated. Although the incidence of partial or total hypopituitarism is additive, the combined use of transsphenoidal hypophysectomy with clear definition of the tumor mass and confirmation of the presence of tumor invasion, followed by APPI, appears to be the optimal approach for grade III and IV lesions.

The availability of new generation CT scans should substantially improve treatment planning and further improve precise localization of radiation to the desired tumor volume. Such treatment plans should considerably improve the results of treatment while substantially reducing the incidence of hypopituitarism.

With the improved definition of tumor masses and the ability to collimate charged particle beams accurately, localized tumor destruction using a highly focused microbeam of proton or helium ions or heavier ions (21) such as carbon stereotactically delivered, may eventually be the optimal method for many cases in which selective microadenoma destruction is desired.

Table 5 shows the age and sex of the patients, and Table 6 summarizes all patients with pituitary tumors treated by us.

BIBLIOGRAPHY

1. Recent Advances in the Diagnosis and Treatment of Pituitary Tumors, edited by John A. Linfoot, Raven Press, New York, 1979. 1140 Avenue of the Americas, New York, New York 10036.

2. History of Pituitary Therapy at Donner Laboratory. J.H. Lawrence, Recent Advances in the Diagnosis and Treatment of Pituitary Tumors (J.A. Linfoot, editor), New York, Raven Press, p. 1.

3. Tobias, C.A., Lawrence, J.H., Born, J.L., McCombs, R.K., Roberts, J.E., Anger, H.O., Low-Beer, B.V.A., Huggins, C.B.: Pituitary Irradiation with High Energy Proton Beams: A Preliminary Report. Cancer Res. 18:121, 1958.

4. Lawrence, J.H., Tobias, C.A., Linfoot, J.A., Born, J.L., Lyman, J.T., Chong, C.P., Manougian, E., and Wei, W.C.: Successful Treatment of Acromegaly: Metabolic and Clinical Studies in 145 Patients. J. Clin. Endrocrinol. and metabolism 31:180-198, 1970.

5. Linfoot, J.A., Lawrence, J.H., Born, J.L. and Tobias, C.A.: The Alpha Particle or Proton Beam in Radiosurgery of the Pituitary Gland for Cushing's Disease. New Engl. J. Med. 269-597-601, 1963.

6. Linfoot, J.A., Nakagawa, J.S., Wiedemann, E., Lyman, J., Cong, C., Garcia, J., Lawrence, J.H.: Heavy Particle Therapy: Pituitary Tumors. Bull. Los Angeles Neurological Societies 42 (3-4):175-189, 1977.

7. Linfoot, J.A., Cong, C.Y., Lawrence, J.H., Born, J.L., Tobias, C.A., Lyman, J.: Acromegaly, pp. 191-246 in Hormonal Proteins and Peptides, Vol. III, C.H. Li (ed.), Academic Press, Inc., 1975.

8. Kjellberg, R.N., Sweet, W.H., Preston, W.M., Koehler, A.M.: The Bragg Peak of a Proton Beam in Intracranial Therapy of Tumors. Trans. Am. Neurol. Assoc. 87:216, 1962.

9. Linfoot, J.A., Garcia, J.F., Wei, W., Fink, R., Sarin, R., Born, J.L., Lawrence, J.H. Human Growth Hormone Levels in Cerabrospinal Fluid. J. Clin. Endocrinol. Metab. 31:230, 1970.

10. Ganguly, A., Stanchfield, J.B., Roberts, T.S., West, C.D., Tyler, F.H.: Cushing's Syndrome in a Patient with an Empty Stomach Sella Turcica and a Microadenoma of the Adenohypophysis. Am. J. Med. 60:306, 1976.

11. Ludecke, D., Kautzky, R., Saeger, W., Schrader, D.: Selective Removal of Hypersecreting Pituitary Adenomas. Acta Neurochir (Wien) 35:27, 1976.

12. Sheline, G.E.: Role of Conventional Radiation Therapy in the Treatment of Functional Pituitary Tumors. In: Linfoot, J.A. (ed.) Recent Advances in the Diagnosis and Treatment of Pituitary Tumors. Raven Press, New York, p. 289, 1979.

13. Hardy, J.: Transsphenoidal Microsurgical Removal of Pituitary Microadenoma. In: Morley J.P. (ed.), Progress in Neurological Surgery. Saunders, Philadelphia, p. 377, 1976.

14. Wilson, C.B., Tyrell, J.B., Fitzgerald, P.A., Pitts, L.H.: Cushing's Disease and Nelson's Syndrome. Reprinted from Clinical Neurosurgery, Vol. 27. The Congress of the Neurological Surgeons, USA. 1980.

15. Wilson, C.B., Tyrell, J.B., Fitzgerald, P.A., Forsham, P.H.: Cushing's Disease: Surgical Management. The Departments of Neurological Surgery and Medicine, and the Metabolic Research Unit, University of California, San Francisco. Year Book Medical Publishers, Inc. 1982.

16. Baskin, D.S., Boggan, J.E., Wilson, C.B.: Transsphenoidal Microsurgical Removal of Growth Hormone-Secreting Pituitary Adenomas. Journal of Neurosurgery 56:634-641, 1982.

17. Kjellberg, R.N., Kliman, B.: Radiosurgery Therapy for Pituitary Adenoma, pp. 459-478 in: The Pituitary Adenoma, Kalmon, D.P., Jacson, I.M.D., Reichlin, S., editors. Plenum Publishing Corporation, N.Y., 1980.

18. Goldin, L.L., Chuviloo, I.V., and Ruderman, A.E.: Application of Charged Heavy Particles in Medicine. Joint Institute for Nuclear Research, Report JINR 18-82-117, Dubna, USSR.

19. Aristizabal, S., Caldwell, W.L., Avila, J.: The Relationship of Time-Dose Fractionation Factors to Complications in the Treatment of Pituitary Tumors by Irradiation. Int. J. Radiat. Oncol. Biol. Phys. 2:667, 1977.

20. Linfoot, J.A.: Alpha Particles Versus Conventional Radiotheraphy to the Pituitary Region: A Comparison of Risk Benefit. Clin. Neurosurg. 27:83, 1980.

21. Chatterjee, A., Alpen, E.L., Tobias, C.A., Llacer, J., Alonso, J.: High Energy Beams of Radioactive Nuclei and their Biomedical Applications. Int. J. Radiation Oncology Bio. Phys. Vol. 7, pp. 503-507, 1981.

Table 1. Replacement therapy in acromegaly: adrenal replacement

Adrenal replacement	% Patients
APPI primary treatment	
No replacement	65
"F" prior to APPI	1
"F" after APPI[a]	34
Total	100
Surgery prior to APPI	
No replacement	29
"F" prior to APPI	37
"F" after APPI[b]	34
Total	100

[a]Replacement time average 4.3 years (range 0.2 to 12 years).
[b]Replacement time average 3.0 years (range 0.2 to 14.7 years).

Table 2. Replacement therapy in acromegaly: thyroid replacement

Thyroid replacement	% Patients
APPI primary treatment	
No replacement	61
T_4 prior to APPI	6
T_4 after APPI[a]	33
Total	100
Surgery prior to APPI	
No replacement	31
T_4 prior to APPI	41
T_4 after APPI[b]	28
Total	100

[a]Replacement time average 3.9 years (range 0.2 to 11.3 years).
[b]Replacement time average 3.5 years (range 0.7 to 15.4 years).

Table 3. Replacement therapy in acromegaly: gonadal replacement

Gonadal replacement	% Patients
APPI primary treatment	
No replacement	73
E/T prior to API	2
E/T after APPI[a]	25
Total	100
Surgery prior to APPI	
No replacement	49
E/T prior to APPI	22
E/T after APPI[b]	29
Total	100

E = estrogen. T = testosterone.
[a]Replacement time average 4.1 years (range 0.2 to 12.0 years).
[b]Replacement time average 2.5 years (range 0.9 to 10.9 years).

Table 4.

CAUSE OF DEATH	NUMBER OF PATIENTS	SURVIVAL POST-Rx
Cardiovascular/cerebrovascular disease	27	0.5-21.8
Systemic Histoplasmosis	1	3.8
Acute Myelogenous leukemia	1	4.1
Drug Overdose	2	1.6, 4.0
Suicide	1	0.6
Meningioma	1	10.8
Bleeding Duodenal Ulcer	1	0.2
Post-surgery	4	2.8-5.8
During surgery	1	3.2
Acute Renal Failure	1	11.1
Metastatic Cancer (breast, lung)	4	0.4-22.9
CNS (exact cause?)	1	16.3
Organic Brain Syndrome*	1	6.6
Accidental (choking, vehicular accident)	2	2.9, 11.0
TOTAL	48	

*As previously reported, this patient was lost to follow-up; at another clinic, he was inadvertently given a series of pituitary photon irradiation.

Table 5. This table illustrates the fact that acromegaly occurs more commonly in males, and that there is usually a long delay before these patients are referred for treatment.

AGE AND SEX DISTRIBUTION OF PATIENTS WITH ACROMEGALY TREATED WITH HEAVY PARTICLE PITUITARY IRRADIATION

PATIENTS		AGE (Years)		DURATION (Years)
Sex	Number	At time of heavy-particle therapy	At time of onset of signs and symptoms	At time of heavy-particle therapy
		Median (Range)	Median (Range)	Median (Range)
MALE	191	40.2 (15–69)	31.1 (13–64)	7.6 (1–40)
FEMALE	121	48.3 (15–68)	36.8 (13–63)	9.0 (1–29)
TOTAL	312	42.6 (15–69)	34.5 (13–64)	8.1 (1–40)

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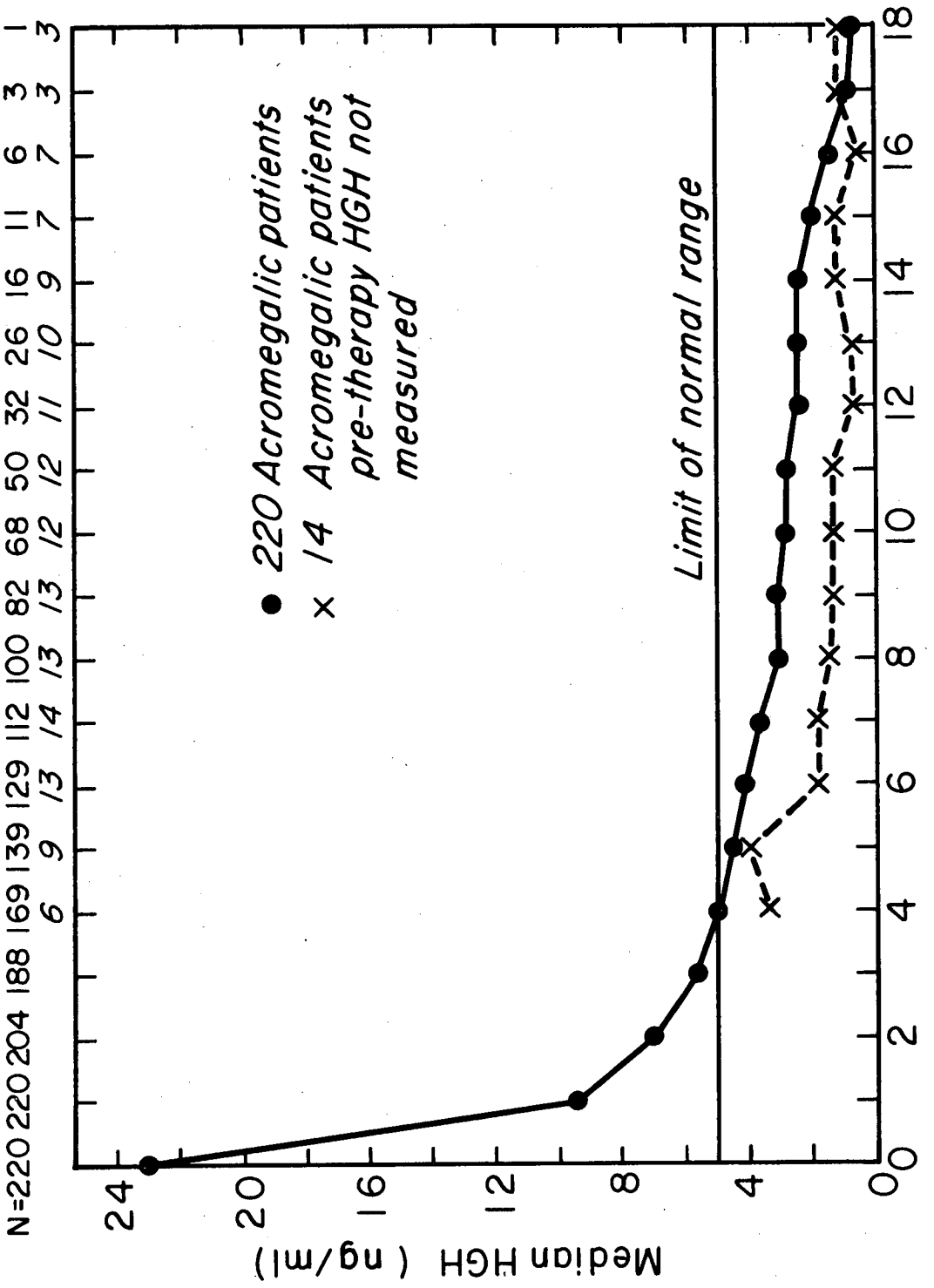
Table 6. Patients with pituitary tumors treated with heavy particle irradiation, Feb. 1958 - Oct. 1979.

				SURVIVAL --- YEARS POST RX											
				1 year		3 years		5 years		10 years		15 years		20 years	
	Total	Living	Dead	Live	At Risk	Live	At Risk	Live	At Risk	Live	At Risk	Live	At Risk	Live	At Risk
ACROMEGALY	314	275	39	309	314	297	307	268	290	152	179	50	83	11	49
CUSHING'S	80	76	4	79	80	74	76	51	53	20	23	9	13	1	5
NELSON'S	17	16	1	17	17	17	17	12	13	6	7	3	4	1	2
CHR.AD.	34	27	7	34	34	31	34	27	32	14	20	7	14	2	9
PROLACTIN	22	22	0	22	22	22	22	15	15	2	2	1	1	--	--
	467	416	51	461	467	441	456	373	403	194	231	70	115	15	65

Fig. 1. Changes in plasma growth hormone level in 234 patients with acromegaly who have been reevaluated one or more years after completion of HPPI. The Ns at the top of the graph indicate the number of individuals used in calculating median for each time-interval. Fourteen patients did not have pre-treatment growth hormone determinations by radioimmunoassay, but their growth hormone levels determined 4 to 18 years after treatment (note X--X--X) are consistent with the other 220 patients. These data are for patients who had HPPI only. Excluded were 63 patients (20.1% of the entire group) who had undergone prior pituitary surgical procedures, and 5 patients (1.6% of the entire group) whose pre-treatment growth hormone levels were less than 5 ng/ml. The 20 patients who subsequently underwent a second pituitary procedure (surgical hypophysectomy or irradiation) were included until the time of the second procedure.

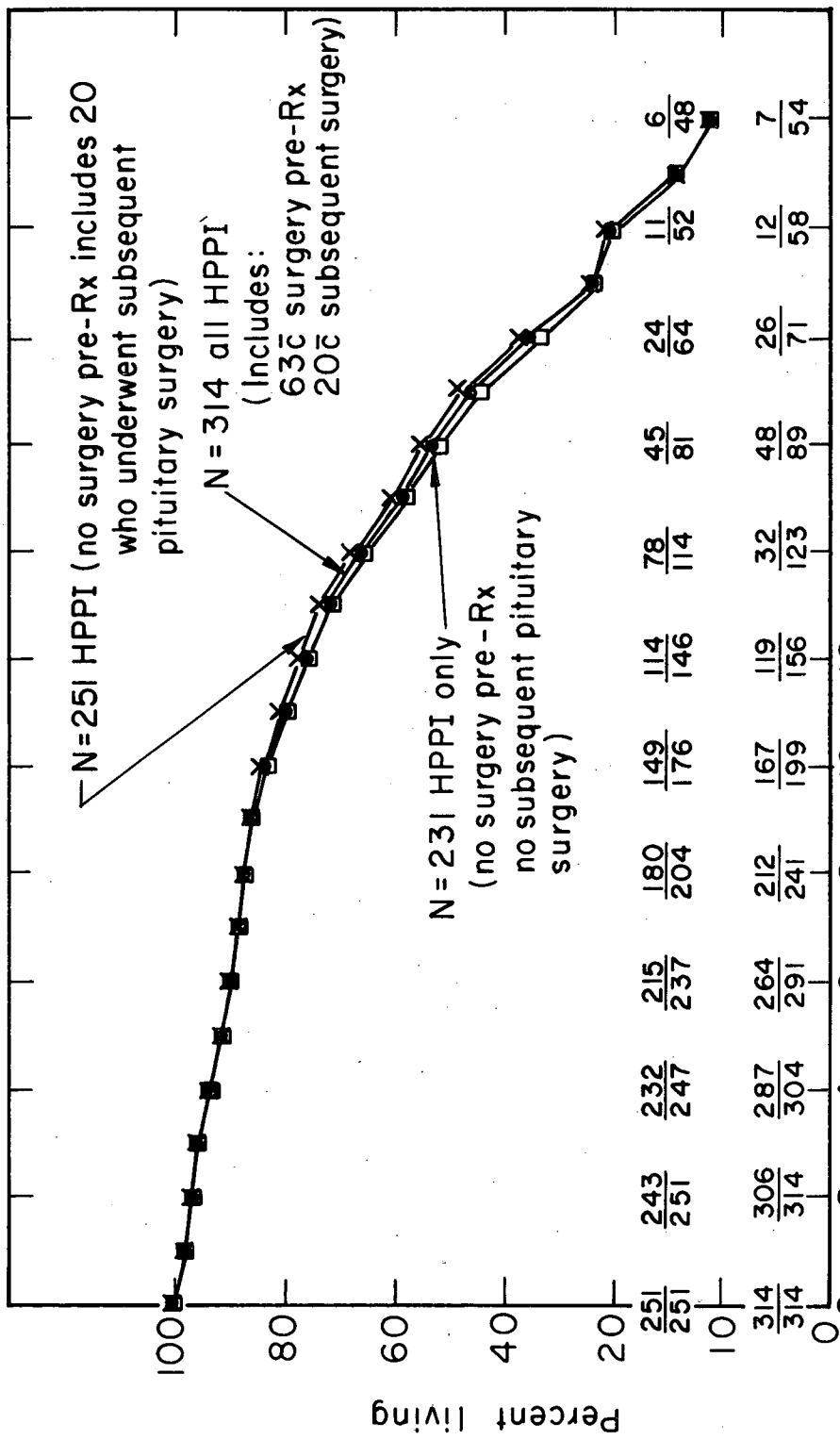
Figs. 2 and 3. Figures 2 and 3 are based on follow-up on the 314 patients with 93% follow-up (1958-1978). The balance are presumed living, but we do not have complete follow-up information. In the graphs of survival their slopes will be little changed, however. 63 patients had pituitary surgery prior to HPPI; 251 of these 314 patients had HPPI only as primary treatment; 20 of the latter had post-HPPI pituitary surgery. Since the majority of the patients are alive, the curves in

Fig. 3. (cont.) Fig. 3 will continue to approach the several curves of the age sex-matched tested diabetic population and the general population.



XBL829-4115

Fig. 1



XBL832-3626

Fig. 2

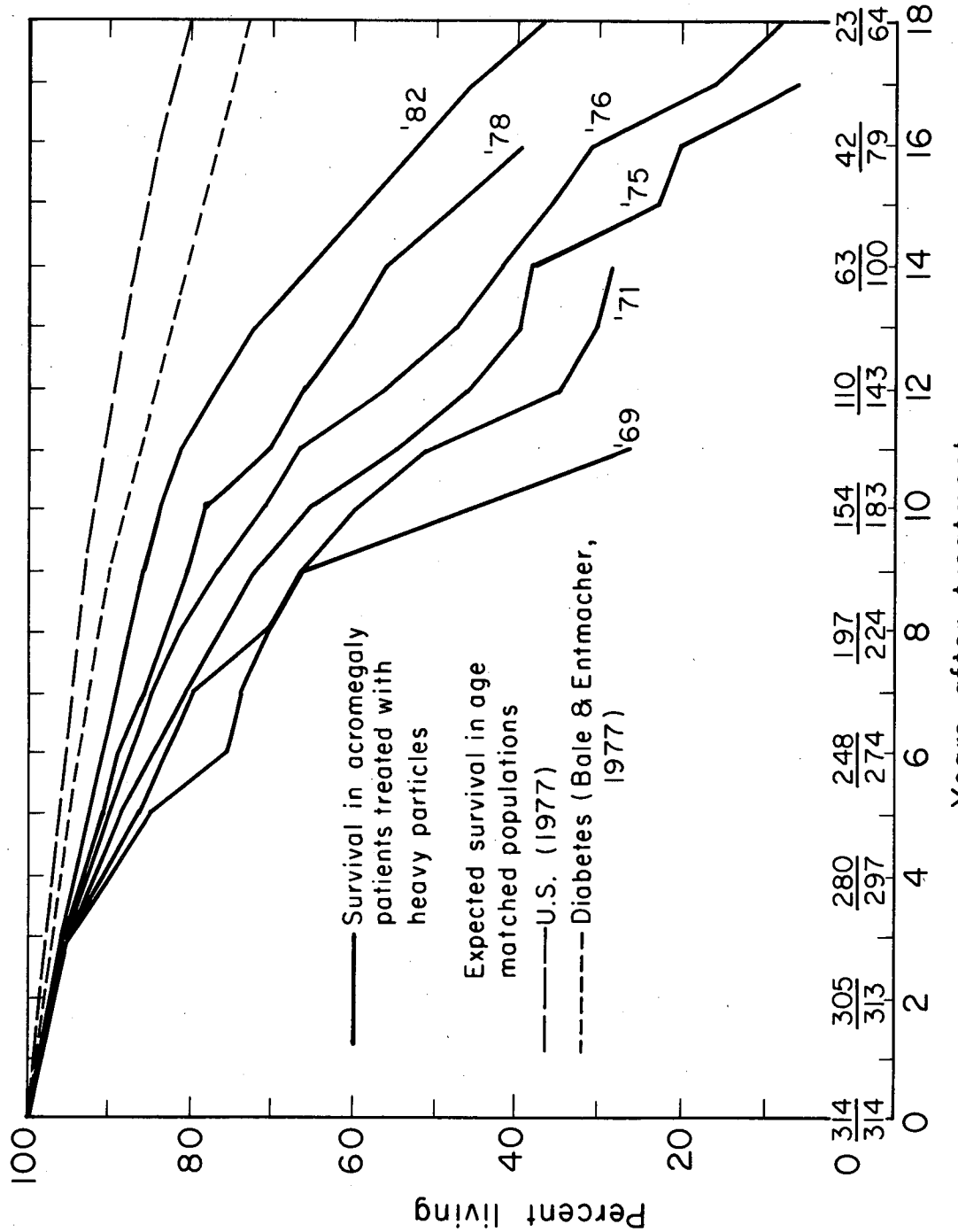


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Fig. 3

PART III

HEAVY CHARGED PARTICLE RADIOTHERAPY FOR MALIGNANT GLIOMA OF THE BRAIN

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Heavy charged particles offer significant potential advantages for treatment of malignant glioma of the brain. Physical parameters of heavy charged particle beams offer the opportunity to conform the extended Bragg peak to the tumor target volume with less delivery of dose to adjacent portions of the brain outside of the tumor bearing area (11). This physical dose advantage is increased by the higher level of biological effectiveness in the stopping region where most of the heavy charged particle high LET events occur. Thus, the increased RBE in this region represents the ratio of biologically effective dose delivered to the tumor relative to surrounding normal tissues. Lighter charged particles such as protons and helium ions offer physical dose advantages because of sharp lateral and distal edges of the beam. However the amount of high LET present within these beams

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is not sufficient to distinguish them radiobiologically or clinically from low LET megavoltage photon beams, at least so far as present radiobiological and clinical studies demonstrate. Heavier charged particles such as nuclei of atomic number 10-15 offer improved biological advantage over light particles specifically in depression of the oxygen effect in the region of the extended Bragg peak, diminished variations in sensitivity during different phases of the cell division cycle, depressed enzymatic repair mechanisms, greater than expected delays in cell division and decreased protective effects of neighboring cells in organized systems (1-4,12). Because of the greater amount of fragmentation and range straggling in the heavier beams, a significant although reduced dose distal to the stopping point of the heavy charged particle beam will be encountered. Nevertheless compared to exponentially decaying ionizing radiation such as photons or neutrons, the dose localization advantage will lie with heavy charged particle, particularly when appropriately modified to maximize the biologically effective dose in the target volume relative to other areas of normal brain. For tumors such as glioblastoma and anaplastic astrocytoma, precise dose localization such as is available with protons or helium is not required since present methods of tumor localization are not sufficient to avoid utilizing a significant volume of clinically univolved tissue (ordinarily 2 centimeters in dimension) as a margin so that the target volume includes possible microscopic extension. Thus, heavy charged particles with atomic numbers between 10-15 offer an attractive

approach since such beams should retain significant biological potential and still have sufficient physical attributes to be of advantage in tumors such as one would encounter within the brain (11,16). The optimum method of using such heavy charged particle beams has not yet been developed. At present preliminary studies have been done with lighter ions ranging from helium through neon utilizing fixed ridge filters to spread the beam and significant amounts of absorber to spread the beam to a clinically useful diameter. In the future, fragmentation effects can be diminished by alternative methods of beam spreading. Optimization of beam delivery will probably require development of three dimensional beam scanning in order to best minimize dosage to adjacent normal tissues. While completion of such optimization is several years in the future, we have begun preliminary studies at the Lawrence Berkeley Laboratory utilizing heavy particle beams in the treatment of anaplastic astrocytoma and glioblastoma of the brain. We are mindful of the experience with neutron irradiation of such tumors and the effects of neutrons on normal brain (5-8). While the neutron studies focus at present on searching for the optimal dose-time parameters, we intend to study utilization of heavy charged particles with reduction of dose to normal brain. We will also continue to search for improved fractionation schedules as well as optimization of beam delivery. We are also interested in possible potentiation (3) that might take place between split dose delivery separated by less than thirty minutes in time; such split doses might effectively combine high LET and low LET

irradiation in order to maximize effect on tumor while perhaps protecting normal tissues. Since 1975, fourteen patients with primary malignant glioma of the brain have received part or all of their radiation with neon ions. Six of these patients received boost therapy following photon irradiation, with a small group of 8 patients receiving treatment entirely with neon ions. The RBE and dose selected in these early patients were conservative and consequently the findings to date have not been different from previous low LET megavoltage results with photon irradiation. The longest survival has been 18 months post therapy with a mean survival for the group of 8.3 months and a median of six months. Of the eight patients treated entirely with neon ions, six have tumor recurrence within 14 months after treatment. All of the patients who received partial treatment with neon ions to a reduced volume after photon irradiation have also failed. In the group treated fully with heavy particle irradiation, only 2 of 8 patients remain alive to date with follow-up less than 24 months. Of the six patients dead, five are known to have persistent tumor. One patient died without evidence of presistent tumor but without clear data to indicate that heavy charged particle irradiation brain damage was the cause of death. As this was a Phase I study beginning with a conservative RBE value and gradually escalating doseage, failure because of tumor persistence is understandable. As this study proceeds, further dose escalation will take place with careful clinical and CT follow-up of these patients. We are particularly interested in serial quantitative CT analysis to

look for evidence of altered normal brain function as well as evaluation of tumor status (13). These studies will be augmented by positron emission tomography to be accomplished at the Lawrence Berkeley Laboratory. The efficacy of neutron irradiation in destroying glioblastoma leads one to the optimistic hope that heavy charged particles which share similar biological potential to neutrons can equally well destroy the tumor. The dose localization advantage of heavy charged particles permits the possibility that optimization of beam delivery will allow the level of damage to normal brain structures to be lower than with neutrons thus permiting improved survival. As the tumor itself is one with a propensity to tumor induced neorosis, destruction of the tumor may leave these patients with areas of persistant coagulative neoroses. Improved surgical techniques may be necessary to deal with this problem if longer survival and an improved quality of life is to be found.

Precision High Dose Radiotherapy with Helium Ions

One of the critical areas of radiation oncologic research is that of improving local and regional control of resistant tumors through delivery of more effective radiation therapy. Protons (14) and helium ions (9) possess attractive physical characteristics allowing for the maximum delivery of dose to the target volume with sparing of adjacent normal tissues. There is little increase in relative biological effectiveness and the OER for these beams is virtually the same as for low LET x-ray therapy. Such beams offer value in the treatment of difficult tumors lying close to the spinal cord and/or base of brain

without the possibility of complete surgical resection. Tumors such as chordoma, chondrosarcoma, malignant schwanoma and melanoma of the uveal tract of the eye are among these. At the Lawrence Berkeley Laboratory, helium ions have been tried in a variety of such sites where improved dose localization might constitute a possible advantage. From 1975 through 1981, approximately 85 such patients have completed therapy for:

1) selected tumors round the base of the skull and spinal cord as well as in the paranasal sinuses (26 pts)
2) uveal melanomata (62 pts)

As many have had fairly low grade malignancies, long term follow up is still needed to fully evaluate tumor control and complications. Our goal has been to deliver a minimum dose of 60 to 75 Gray-equivalents at 2.0 GyE per fraction, four fractions per week while keeping the dose to the spinal cord, brain stem or small volumes of the brain to below 50 GyE wherever possible. Because the precision of these techniques is gauged in millimeters rather than centimeters, this approach should generate new information concerning the morbidity of small volumes of the spinal cord or brainstem receiving doses higher than the usually accepted levels. The following table presents preliminary data for patients with juxtaspinal tumors or tumors at the base of brain (Table 1).

Ocular Melanoma

Uveal melanomas or other eye tumors are also good candidates for precision high dose protons or helium charged particle therapy. These tumors are precisely localized for radiotherapy by ultrasound, CT scanning, fundoscopic examination and photography, and by attachment of radioopaque tantalum 2.0 mm. diameter rings on the sclera around the base of the tumor. With precisely delivered charged particle radiotherapy such as with protons, helium or carbon ions, a high uniform dose can be delivered to the tumor with little dose to critical structures such as optic disc and fovea centralis unless the tumor is within three millimeters of them. For patients with uveal melanomas doses of 50-90 Gray-equivalents have been delivered in 5 fractions over 7 to 10 days with protons and helium ions (9,14). At Lawrence Berkeley Laboratory, we have completed treatment in 62 patients with uveal melanoma with followup ranging from 1 to 5 years, with a median of 18 months. Twenty patients received 70 GyE in five fractions with failure to control the tumor in one patient due to unknown cause, in two from technical errors and in one patient from multifocal disease. The median survival in this group is 31 months with 11 of 20 patients retaining useful vision. Forty-two patients received 80 GyE in five fractions with failure to control the tumor in one patient. A second patient required enucleation because of glaucoma following irradiation of a very large lesion. The median survival in this group of patients is 15 months with useful vision preserved in 29 of 42 patients. Thus the overall radiation local control rate is 56/62 or 90% as shown in Table II. Normal tissue

effects has been mild, most commonly consisting of mild epitheliitis of the eyelid and loss of lashes in those cases where the lid cannot be fully retracted out of the radiation field. Two patients have developed cataracts which are not affecting their vision significantly as yet. One patient, with a very large tumor, had shrinkage of the tumor, but severe pain secondary to glaucoma and retinal detachment required enucleation. We are continuing study of different dose levels and treatment schemes in order to optimize techniques which might control uveal melanoma lying quite close to or actually infiltrating the optic nerve or fovea centralis, while preserving useful vision. To date, the rate of metastases in this series remains low (2/62) although further followup is required to learn if avoiding enucleation in these patients is helpful in diminishing spread of tumor.

REFERENCES

1. Tobias, C. A., et al.; Molecular and cellular radiobiology of heavy ions. International Journal of Radiation Oncology, Volume 8, Number 12, December 1982, pp. 2109-2120.

2. Fu, K. and Phillips, T. L.: The relative biological effectiveness and oxygen enhancement ratio of neon ions for the EMT6 tumor system. Radiology 120:439-441, 1976.

3. Ngo, F., Blakely, E. and Tobias, C.: Sequential exposure of mammalian cells to low and high LET radiations. Radiation Research 87:56-78, 1981.

4. Roots, R., Yang, T., Craise, L., Blakely, E. and Tobias, C.: Rate of rejoining of DNA breaks induced by accelerated carbon and neon ions in the spread Bragg peak. International Journal of Radiation Biology 38:203-210, 1980.

5. Catterall, M., et al.: Fast neutrons compared with megavoltage X-rays in the treatment of patients with supertentorial glioblastoma. International Journal of Radiation Oncology, Biology, and Physics 6:261-266, 1980.

6. Tsunemoto, H.: Japanese experience with clinical trials of fast neutrons. International Journal of Radiation Oncology, Volume 8, pp. 2169-2172, December 1982.

7. Laramore, G., Griffin, T., Gerdes, A., Groudine, M. and Parker, R.: Fast neutron and mixed beam teletherapy for grades II and IV astrocytomas. Cancer 42:96-103, 1978.

8. Griffin, T., Laramore, G., Hussey, D., Hendrickson, F., and Rodrigues, A.: Fast neutron beam radiation therapy in the United States. International Journal of Radiation Oncology, Volume 8, Number 12, December 1982, pp. 2165-2168.

9. Castro, et al.: Treatment of cancer with heavy charged particles. International Journal of Radiation Oncology, Volume 8, Number 12, December 1982, pp. 2191-2198.

10. Castro, J. R., Quivey, J. M., Lyman, J. T., Chen. G. T. Y., Phillips, T. L., Tobias, C. A., and Alpen, E. L.: Current Status of Clinical Particle Radiotherapy at Lawrence Berkeley Laboratory. Cancer, 46:633-641, 1980.

11. Chen, G. Y. T., Castro, J. R. and Quivey, J. M.: Heavy Charged Particle Radiotherapy. Ann. Rev. of Biophysics and Bioengineering, Vol. 10, pp. 419-429, 1981.

12. Tenforde, T. J., Afzal, S. M., Parr, S. S., Howard, J., Lyman, J. and Curtis, S. B.: Cell Survival in Rat Rhabdomyoscarcoma Tumors Irradiated in vivo with Extended Peak Silicon Ions. Radiation Research 92, 208-216 (1982).

13. Fike, John R., Cann, C. E., Davis, R. L., and Phillips, T. L. Radiation effects in the canine brain evaluated by quantitative computed tomography. Radiology, Vol. 144, Number 3, pp. 603-608.

14. Suit, H., Goitein, M., Munzenreider, J., Verhey, L., Blitzer, P. Gragoudas, E., Koehler, A., Urie, M., Gentry, R., Shipley, W., Urano, M., Duttenhaver, J. and Wagner, M.: Evaluation of the Clinical Applicability of Proton Beams in Definitive Fractionated Radiation Therapy. Int. J. Rad. Oncology, Vol. 8, No. 12, December 1982, pp. 2199-2205.

Table 1. Precision high dose therapy with heavy charged particles at Lawrence Berkeley Laboratory for juxtaspinal or base of skull tumors.

Site	Status		Tumor Dose	Median Survival
	Pts	Local Control		
Sacrum	6	4	70-75 GyE	20 mos (10-67)
Clivus	9	8	36-74 GyE	19 mos (3-60)
Base of Skull, Paranasal Sinus	7	5	42-70 GyE	12 mos (5-66)
Juxtaspinal Tumors	4	4	36-70 GyE	7 mos (4-17)
TOTALS	26	21 (81%)		

Table II. Uveal melanomata treated with helium ion radiotherapy.

	1977-1982			
Dose	Number Patients	Failure	Useful Vision	Mean Survival
70 GyE	20	4	11/20	25 mos
80 GyE	42	2	29/42	10 mos
Totals	62	6(10%)	40/62	17 mos

PART IV

STEREOTACTIC HEAVY-ION BRAGG PEAK RADIOSURGERY FOR INTRACRANIAL VASCULAR DISORDERS

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Recent advances in diagnostic and microsurgical techniques have made direct neurosurgical treatment of certain intracranial vascular disorders safer and more successful. Surgical treatment of poorly accessible deep arteriovenous malformations (AVMs), including carotid-cavernous fistulas, involves total excision, where possible, or combined with ligation or intravascular occlusion of feeding arteries. If deep AVMs are inoperable or, where other factors preclude neurosurgery, certain stereotatic radiosurgical techniques to induce vascular thrombosis and obliteration have been tried. It appears that if the small shunting vessels of a deep AVM possess hemodynamic flow conditions which differ from flow in normal vessels, then focal-beam irradiation of these shunting vessels can lead to thrombosis and hemostasis in the AVM with eventual complete obliteration. Leksell (1) and his colleagues at the Karolinska Sjukhuset, Stockholm, introduced stereotatic radiosurgery for inoperable intracranial vascular and other disorders; they use focal gamma radiation from a specially-designed unit with 179 cobalt-60 sources, giving rise to narrow irradiation beams, stereotactically-directed to a small volume within the brain (2). Patients with deep AVMs receive a single or

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multiple treatments; presently, doses of approximately 50.00 Gy are delivered. In their series of AVM patients thus far treated, in the group in which the entire deep AVM was included in the irradiated field, 81 patients have now gone through 1 year and 63 patients have gone through 2 years of follow-up. Total obliteration of the AVM has occurred in about 85% of patients by 2 years. When the deep AVMs were completely covered by the radiation field, over 90% of the patients benefitted from partial or complete obliteration leading to cure (Steiner, personal communication). Partial recovery, presumably with progress to total obliteration in the future, occurred in 10%. However, focal gamma irradiation is limited in its physical characteristics, primarily due to poor isodose distribution and beam quality, limited size of treatment volume, and precision and accuracy of dose delivered. Initial studies on the feasibility of proton beam-induced narrow focal lesions in the brain were carried out by Larsson and his colleagues at the Gustal Werner Institute Uppsala 185 MeV cyclotron. Kjellberg and his colleagues (3) introduced stereostactic proton beam Bragg peak radiosurgical treatment of intracranial deep AVMs at the Harvard 165 MeV cyclotron. Patients receive a single treatment to larger tissue volumes where necessary; presently, doses are usually well below 30.00 Gy equivalent delivered in a single treatment, depending on the location and volume irradiated. The Harvard group has now reported on the follow-up of 205 patients (Kjellberg, personal communication). In 75 patients with 2-17 year follow-up, 63% have thus far demonstrated reduction in the

size of the deep AVM, and 20% have demonstrated complete obliteration. Barcia-Saloria has begun to use a cobalt-60 teletherapy beam at the University of Valencia to induce focal lesions in deep AVMs.

Stereotactic Heavy-Ion Bragg Peak Radiosurgery at Lawrence Berkeley Laboratory. At Lawrence Berkeley Laboratory, patients with inoperable intracranial deep AVMs are treated with stereotactic heavy-ion Bragg peak radiosurgery using focal beams of accelerated 230 MeV/u helium ions at the 184-inch Synchrocyclotron (4). The procedure begins with the fabrication of a vacuum-formed polystyrene head-holder adapted to a modified Leksell-type stereotatic frame for immobilization of the patient during all stereotactic procedures, including cerebral angiography, X-ray computerized tomography and heavy-ion Bragg peak radiosurgery (Figures 1, 2 and 3). Information from the stereotactic cerebral angiography and brain CT scans, together with the raw CT data, are transferred to the computer system in our laboratory for use in interactive charged-particle treatment planning and provides the basis for delivery of stereotactically-directed heavy-ion beams to the AVM target contour within the brain. The stereotactic CT data are used on a pixel-by-pixel basis to design and/or select a collimator aperture for each entry portal; to select the appropriate spread Bragg peak for heavy-ion radiation to contour the stopping region of the heavy-ion beams, and to generate isoeffect and physical dose-distributions overlayed on the CT image for adaptation to stereotactic radiosurgical

treatment with accelerated heavy ions at the Synchrocyclotron. Entry angles and heavy-ion beam ports are chosen to confine the high-dose Bragg peak region to the defined target volume while carefully protecting adjacent normal brain structures.

Method. A finely focused beamline configuration for stereotactic radiosurgery in the brain with the Bragg ionization peak of the 230 MeV/u helium-ion beam has been developed at the 184-inch Synchrocyclotron (5). The helium-ion beam provides improved dose-localization and dose-distribution for stereotactic radiosurgery in all patients with intracranial deep AVMs, including CCFs, thus far treated. Simulation for patient treatment is based on the individual computerized treatment planned stereotactically-directed helium-ion beam dose-distribution calculated from the stereotactic X-ray CT scans and cerebral angiograms. The patient's head is secured in the cyclotron unit by the heavy-immobilizer as part of the ISAH system (Irradiation Stereotactic Apparatus for Humans) (6). Computer-controlled head and beam-positioning can direct the collimated narrow beam to within 0.1 mm as desired within the brain.

The greatest density of stopping heavy ions are concentrated in the deep AVM; the spread Bragg peak is localized so that the amount of radiation to critical adjacent brain structures is less than 10% of the nominal radiation dose. The central AVM dose, the aperture size,

the number of ports, the angulation of the delivered heavy-ion beams, and the spread Bragg peak all determine the isodose contour (Figures 2 and 3). A radiation dose of 45.00 Gy equivalent is delivered to intracranial volumes of from 200 mm^3 up to 25 cm^3; treatment usually occurs through 1 to 3 entry portals, delivered daily for 1 or 2 days, depending on the treatment volume, and the volume of normal brain tissue traversed by the beam. The dose to the critical and sensitive normal brain structures immediately surrounding the AVM is considerably less than 45.00 Gy equivalent; fall-off to 10% of the central dose occurs within 4-6 mm, and is sharper (within 2-3 mm) along the lateral margins of the helium-ion beam (5) (Figures 2 and 3).

Clinical Results. Cerebral angiography, CT brain scanning and EEG studies are carried out prior to radiosurgery and, following radiosurgery, at 6 and 12 month intervals; extended follow-up to 24, 36 and 60 months is planned for each patient as necessary. Clinical objectives are to achieve changes in the intracerebral hemodynamic condition through complete or partial obliteration of the deep AVM resulting in a decrease in neurological deficiencies, subjective complaints or in frequency of seizures. Initial observations in all 36 patients thus far treated indicate that these objectives are being achieved. Radiological objectives are to achieve quantifiable hemodynamic changes, viz., decrease in blood flow through the AVM with decrease in the size of the AVM until total disappearance. It has been observed by the Stockholm group (2) and the Harvard group (3) that hemodynamic changes occur progressively and are usually observed

before morphological vascular alterations. However, in the majority of our patients, significant decrease in the size of the treated deep AVM has occurred.

Certain conclusions can be drawn from our experience with stereotactic heavy-ion Bragg peak radiosurgery in patients with intracranial deep AVMs at the 184-inch Synchrocyclotron at Lawrence Berkeley Laboratory. (1) Whenever possible, surgical excision remains the treatment of choice for intracranial deep AVMs; when deep AVMs are inaccessible and conditions preclude surgery, stereotactic heavy-ion radiosurgery is a safe, reliable and potentially efficienct therapeutic alternative. (2) Stereotactically-directed heavy-ion Bragg peak irradiation is more advantageous than gamma beams, X-ray beams, or proton beams because of much improved spatial definition and dose-distribution of the focal lesion induced in the target volume in the brain. (3) Therapeutic failure results from irradiating some, but not all, of the multiple arterial feeders, or where only a part of the pathological cluster of vessels in irradiated; this has not occurred with our use of helium-ion Bragg peak beams and dose-distributions. (4) Heavy-ion focal beam irradiation of the intracranial deep AVM can induce hemodynamic changes and reduction in the size of the vascular lesion, leading to complete obliteration of the AVM. Neurological changes with improvement have been observed within 3 months, or less; cerebral angiographic changes with decrease in AVM size and flow have been observed within 6 months following radiosurgery. (5) Heavy-ion radiosurgery has proven to be a highly selective method for treatment

of deep vascular structures within the brain. The advantages of the method are: it is a safe noninvasive procedure without any blood loss; patients under threat of hemorrhage from inoperable or inaccessible AVMs can be treated in cases where neurosurgery is unable to help; and prolonged hospitalization is not required. (6) The disadvantages of the method are: obliteration of irradiated deep AVMs does not begin before some 6 months, and sometimes changes require 18 months or more; thus, patients are under threat of hemorrhage for a long time; time-dose-volume-fractionation relationships for heavy-ion focal beam irradiation of brain and other CNS tissues are not fully understood.

REFERENCES

1. Leksell, L. Stereotaxis and radiosurgery - An operative system. Springfield: Charles C. Thomas, 1971.

2. Steiner, L., Backlund, E.O., Greitz, T., Leksell, L., Noren, G., and Rahn, T. Radiosurgery and intracranial arteriovenous malformations. In: Carrea, R., LeVay, D., eds. Neurological surgery with emphasis on non-invasive methods of diagnosis and treatment. Excerpta medica. Amsterdam; 1978: 168-180.

3. Kjellberg, R.N., Poletti, C.E., Roberson, G.H., and Adams, R.D. Bragg peak proton beam treatment of arteriovenous malformations of the brain. In Carrea, R., LeVay, D., eds. Neurological surgery with emphasis on non-invasive methods of diagnosis and treatment. Excerpta medica. Amsterdam: 1978: 181-187.

4. Fabrikant, J.I., Hosobuchi, Y., and Lyman, J.T. Stereotactic heavy-ion Bragg peak radiosurgery for intracranial vascular disorders: Method for treatment of deep arteriovenous malformations. Am. J. Neuroradiol. In press, 1983.

5. Lyman, J.T., Kanstein, L., Yeater, F., Fabrikant, J.I., and Hosobuchi, Y. A helium ion beam for sterotaxic radiosurgery. Am. J. Neuroradiol. In press, 1983.

6. Lyman, J.T. and Chong, C.Y. ISAH: A versatile treatment positioner for external radiation therapy. Cancer 1974; 34: 12-16.

FIGURE LEGENDS

Figure 1. Stereotactic cerebral angiogram for stereotactic helium-ion Bragg peak radiosurgery of an intracranial deep arteriovenous malformation (AVM) in the left frontal cerebral cortex of a 45-year-old woman. (A) and (B): anteroposterior and lateral views demonstrating the left frontal deep 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 X-ray images of the stereotactic cerebral angiograms demonstrating the size, shape and location of the deep AVM in the frontal pole of the cerebral cortex (arrows). (XBB 824-3937A)

Figure 2. Stereotactic helium-ion Bragg peak radiosurgery of the deep AVM illustrated in Figure 1. (A): stereotactic CT scan demonstrating the contrast accumulation in the left frontal region. (B): anteroposterior localization radiograph of the skull illustrating isodensity curves of the stereotactic radiosurgical treatment plan. (C): lateral localization radiograph and isodensity curves of the treatment plan. Multiple-port stereotactic radiosurgery was delivered over 2 days; the dose was 45.00 Gy equivalent, and the volume of tissue receiving greater than 40.00 Gy equivalent is 1440 mm^3. (XBB 826-7006).

Figure 3. Stereotactic helium-ion Bragg peak radiosurgery of a right carotidcavernous fistula (CCF) in a 67-year-old woman. (A) and (B): subtraction images (anteroposterior and lateral views) of stereotactic

cerebral angiogram demonstrating the location and size of the CCF (arrows); the patient is immobilized in the stereotactic head mask and frame. (C): anteroposterior localization radiograph of the skull illustrating isodensity curves of the stereotactic Bragg peak 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 40.00 Gy equivalent, and the volume of tissue receiving greater than 90% of the dose is 280 mm^3. (XBB 800-12345A)

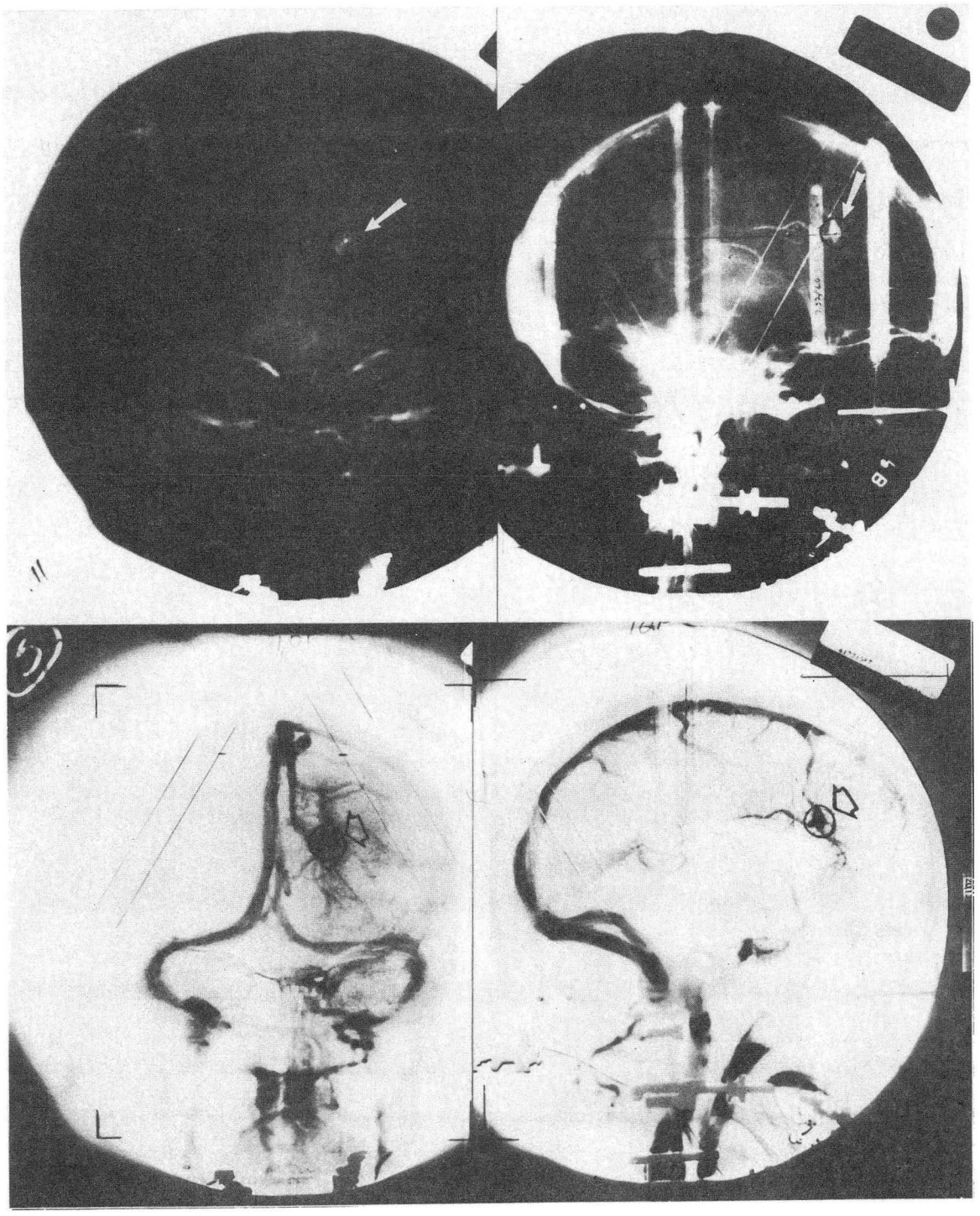

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Fig. 1

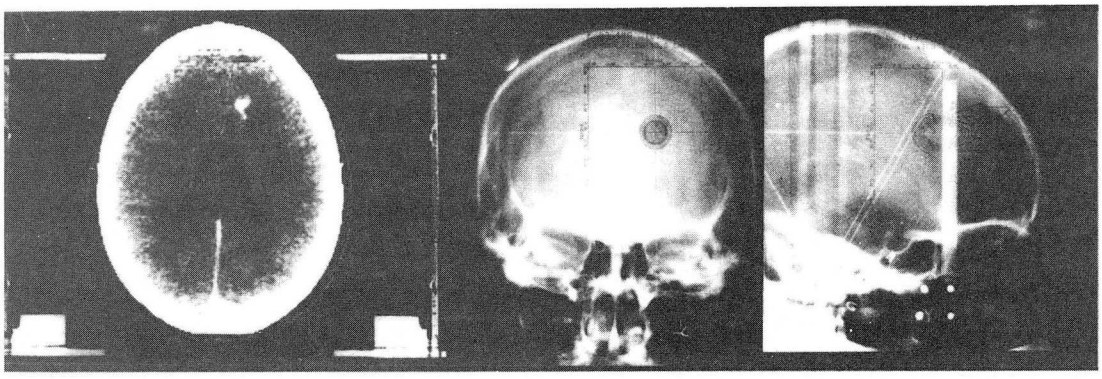

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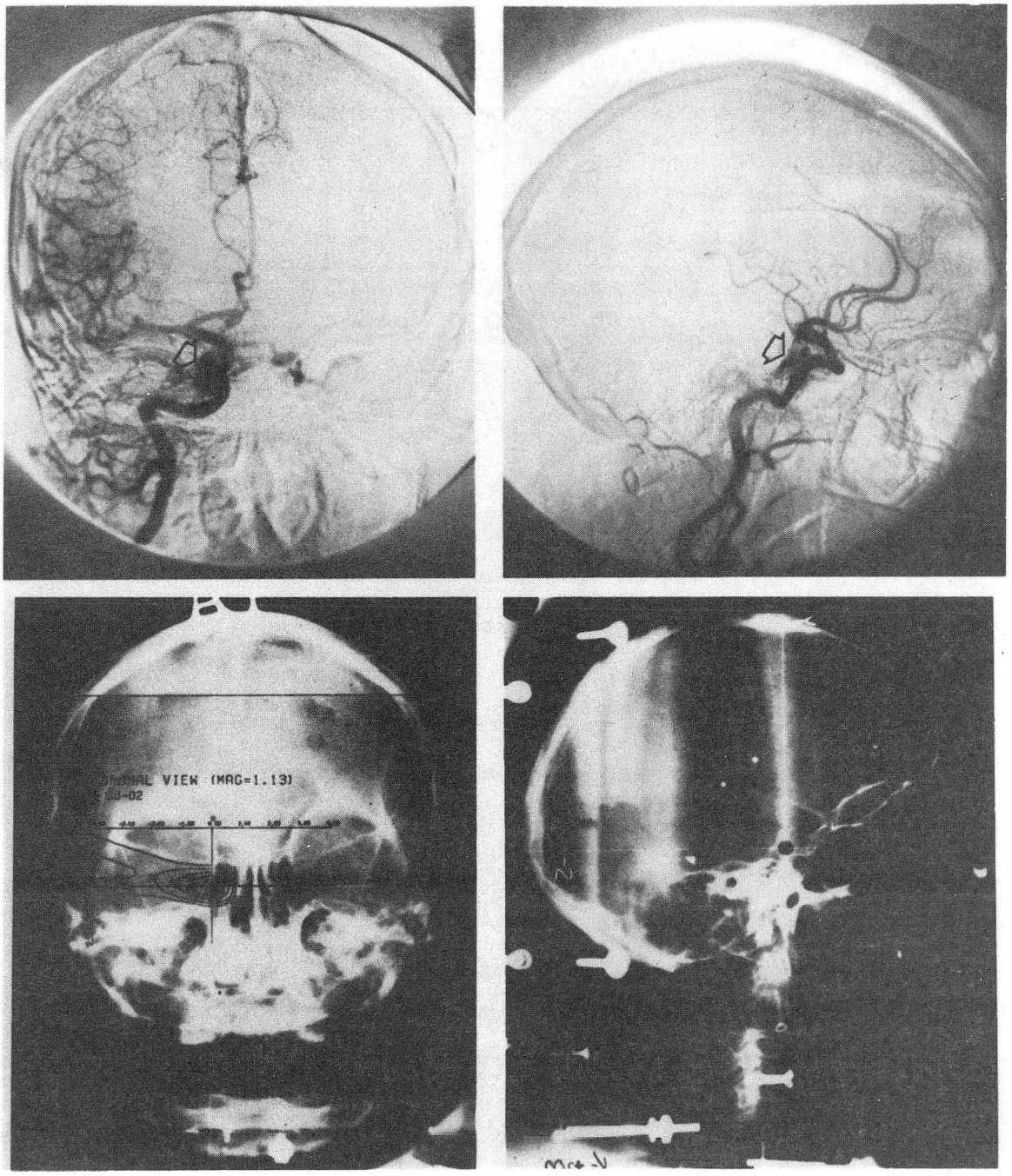
Fig. 2



XBB 800-12345A

Fig. 3

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