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IN NEOPLASTIC AND NEUROLOGIC DISEASE

John H. Lawrence, Cornelius A. Tobias, James L. Born,  
C. C. Wang, and John H. Linfoot

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Donner Laboratory and Lawrence Radiation Laboratory  
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It was stimulating for me to hear Dr. Leksell's paper in which he discussed the tools of the physicist in neurosurgery. His work is an example of international cooperation in research and of the application of atomic energy to medicine. Both Dr. Leksell and I have benefited by collaboration with physical scientists, he with Professor Thé Svedberg, the great Swedish physical chemist who came to Berkeley to plan the building of the Uppsala cyclotron. Likewise, we have had the great help of my brother, Ernest Orlando Lawrence, and of Edwin M. McMillan. Dr. Tobias, head of our team of physicists, spent a year in Uppsala with Professor Svedberg helping prepare their cyclotron for biologic and medical application. Now we are learning much from Dr. Leksell and his associates, who are using the protons from that cyclotron as a neurosurgical tool.

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\*Based in part on a presentation at the Second International Congress of Neurologic Surgery, October 16, 1961, in a discussion of a paper by Professor Lars Leksell of Stockholm, Sweden.

\*\*In the performance of these studies we had the valuable assistance and advice of James Vale in charge of the cyclotron, of John Lyman and Jerry Howard for dose measurements, of Wade Pratt, who expertly made the plastic head masks, and of Drs. Paul Toch, John Green, Lester Lawrence and Robert Weyand, who gave us neurosurgical and radiological consultation.

Our work in this field began in 1935 when we studied the biologic effects of heavy particle radiation in normal and in neoplastic tissues and demonstrated the greater biologic effectiveness of these heavy particles (LET 18 - 20 kev/ $\mu$ ) at that time.<sup>1, 2</sup> Because of this greater RBE, we tried these particles in the therapy of advanced cancer but without encouraging results largely because of the poor depth dose and great scatter of these neutrons.<sup>3, 4</sup> In 1946 when heavy particles with much greater energies became available, Ernest Lawrence, Cornelius Tobias and I considered especially the radiosurgical therapeutic possibilities of protons, deuterons and alpha particles because of their many interesting qualities such as the Bragg curve, their penetrating power, their ability to produce dense ionization in tissue (like the earlier particles we had studied) and their relative lack of scatter when used to bombard tissues. Here we had available a form of radiation that seemed to open a new era in radiation therapy. First, our investigations from 1935 to 1940 had shown that densely ionizing radiation had a greater biologic effect than X radiation on mammalian tissues. Second, with the greater energies of heavy particles now available there was the additional advantage of being able to deliver this dense ionization to great depths in the body with little scatter. There remained one great difficulty - the problem of delineating exactly, in terms of geometry, the tumor or tissue to be irradiated. At that time therefore, we decided against their trial in the therapy of tumors of the brain or lung, or tumors elsewhere within the body.<sup>5</sup>

However, beginning in 1948 in our laboratory, radiosurgical studies with this "atomic knife" (as outlined by Dr. Tobias previously today) demonstrated that, with these high-energy alpha particles, protons or deuterons generated by the 184-inch cyclotron and with rotation techniques

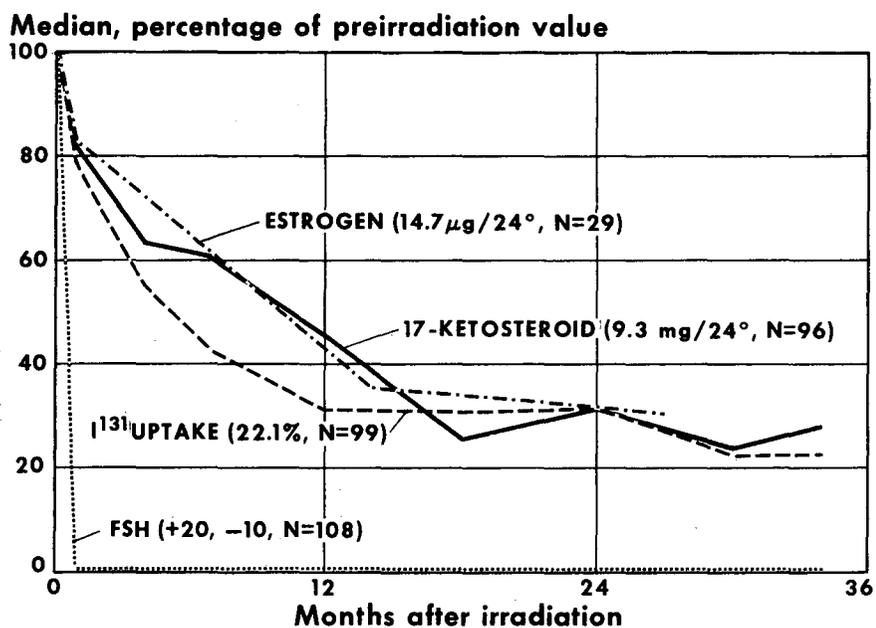
or the Bragg curve, it is possible to produce selective destruction in animal bodies and animal tumors. Using the Bragg curve, it is possible to pass the beam through the body of a mouse and destroy the tumor on the opposite side of the animal.<sup>6</sup> And because the pituitary gland can be accurately located, we began in 1955 to use the beam in humans to suppress the function of the pituitary gland or to destroy the gland, and later to treat other tumors directly.<sup>7, 8, 9</sup> The classification of patients follows.

<u>Patients with:</u>	<u>Number of patients</u>
Cancer of the breast	146
Diabetes mellitus with retinopathy	57
Acromegaly	19
Cancer of the prostate	3
Chromophobe adenoma	2
Malignant exophthalmos	2
Other diseases including brain tumors and soft tissue carcinoma treated directly	7
Total	236

There are 236 patients in the series, including those with advanced metastatic carcinoma of the breast, metastatic carcinoma of the prostate, malignant exophthalmos, malignant diabetes with retinopathy, Cushing's Disease, various forms of pituitary tumors including acromegaly and tumors of the brain or soft tissues.<sup>7, 10, 11</sup>

The largest group consisted of patients with metastatic carcinoma of the breast. After pituitary irradiation there develops evidence of pituitary ablation similar to that seen after surgical hypophysectomy, as judged by changes in various target-organ hormone outputs revealed by thyroid iodine<sup>131</sup> uptake, urinary estrogens, steroids and gonadotropins.

### PITUITARY IRRADIATION - BREAST CANCER



MU - 24882

Fig. 1. Postirradiation estrogen, 17-ketosteroid, iodine <sup>131</sup> uptake and urinary gonadotropin values for patients with metastatic carcinoma of the breast.

In addition, the objectively judged regression in breast carcinoma approximates that following surgical removal of the pituitary gland. Some of the patients have done quite well. For example, 1 patient lived 5 yrs, 9 mos after irradiation; 2 are still living 4 yrs after therapy; 4 survived 3 yrs (3 are still living); 5 survived 2 yrs (1 is still living); 21 survived 1 yr (4 are still living).

Of 57 patients with malignant diabetes mellitus with retinopathy, 47 are living. The median insulin requirement of 45 units prior to irradiation dropped to 25 units afterwards, demonstrating a marked decrease in need. Several patients required no insulin following pituitary irradiation. The changes in retinopathy following irradiation were studied, and stabilization was observed in 25 patients and progression in 17 (13 patients had not been reevaluated). Visual acuity improved in 14 patients, remained unchanged in 14 and decreased in 17. Retinal photographs were taken in all cases prior to and at various time periods after pituitary irradiation. Some of the patients showed improvement in the objective retinal findings that will be reported in detail later. These results, although not remarkable, give one some encouragement to pursue this work. Most of the patients thus far treated have had advanced degrees of diabetic retinopathy, often with severe nephropathy and cardiovascular disease.\* Now we are treating patients with earlier forms of retinopathy and those with little or no nephropathy or severe vascular complications, and we expect more encouraging results.

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\*Of the 10 deceased diabetics, all initially had nephropathy and/or cardiovascular disease; 5 of them died of uremic complications and 3 of acute myocardial infarction.

We have treated 19 patients with acromegaly and 2 with chromophobe adenoma. It is important to recognize that, in spite of the many great advances in therapeutic endocrinology and neurosurgery, there is not a completely successful treatment for acromegaly. Relief of symptoms and signs for long periods of time are not achieved often, and life expectancy is not good.<sup>12</sup> Because in the past about half of the patients died before the age of 50, investigators are attempting to refine and extend techniques of irradiation, surgery and endocrine therapy. Often in the past, those patients receiving X radiation were given doses in the range of 2,000 to 4,000 rad over a period of one month. The danger of cranial nerve and brain damage precluded the use of larger doses. In 1935, while working with Dr. Harvey Cushing we reviewed the literature on the effects of pituitary irradiation and carried out a series of experiments confirming the radio-insensitivity of the pituitary gland to the techniques of irradiation then available,<sup>13</sup> but now, with such high energy particulate radiation as 900-million-volt alpha particles, much greater doses can be given safely.<sup>9</sup> Of the 18 acromegalic patients now living, 11 were treated more than 2 years ago. The 2 patients with chromophobe adenoma, one treated 24 months ago and one 21 months ago, are alive. These patients are much improved subjectively and objectively. One patient with long-standing acromegaly died of cardiomegaly and coronary occlusion 3-1/2 years after treatment. Three of the acromegalic patients, who prior to irradiation were taking insulin for diabetes mellitus, no longer require the insulin. In addition, growth hormone assays after irradiation show marked decrease in the level of serum growth hormone values.

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\*Professor C. H. Li, personal communication.

Similarly, urinary estrogens, gonadotropins, 17-ketosteroids and 20,21-ketols, as well as iodine<sup>131</sup> uptake and serum phosphorus, were decreased. Elevated levels of urinary estrogens in the male acromegalics prior to pituitary irradiation are a new finding. From these preliminary observations it seems probable that future work will result in extension of life and better control of acromegaly by heavy-particle pituitary irradiation. There have been no radiosurgical complications in this group of patients.

Some neurologic complications resulted in those patients who received relatively large doses of radiation, especially in patients with advanced breast cancer; <sup>14, 15</sup> of these, 6 had serious damage to the cranial nerves, 5 had temporal lobe damage resulting in temporal lobe seizures that were easily controlled with anti-convulsant drugs until recurrence of metastatic growth and the patient's death. A complete study of the gross and histologic findings in the pituitary and brain of those patients with advanced breast cancer coming to postmortem is now in preparation. However, during the past few years, since we began giving total dosages of 9000 to 11,000 rad or less in 11 days to the center of the pituitary of patients with malignant diabetes with retinopathy and 5,000 to 7,000 rad in 11 days to patients with acromegaly and pituitary adenomas, we have not seen these complications.

Figure 2 shows pre- and post-irradiation photographs of a patient with malignant exophthalmos who was treated with heavy particle radiation (10,000 rad in 11 days). The picture on the right shows the marked decrease in the periorbital edema and exophthalmos two years after irradiation, and the patient remains well 3 years post-irradiation.



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Fig. 2. Photographs of a patient treated with 10,000 rad for severe exophthalmos. Photograph on left is before irradiation.

As examples of the use of the Bragg curve the following cases are presented.

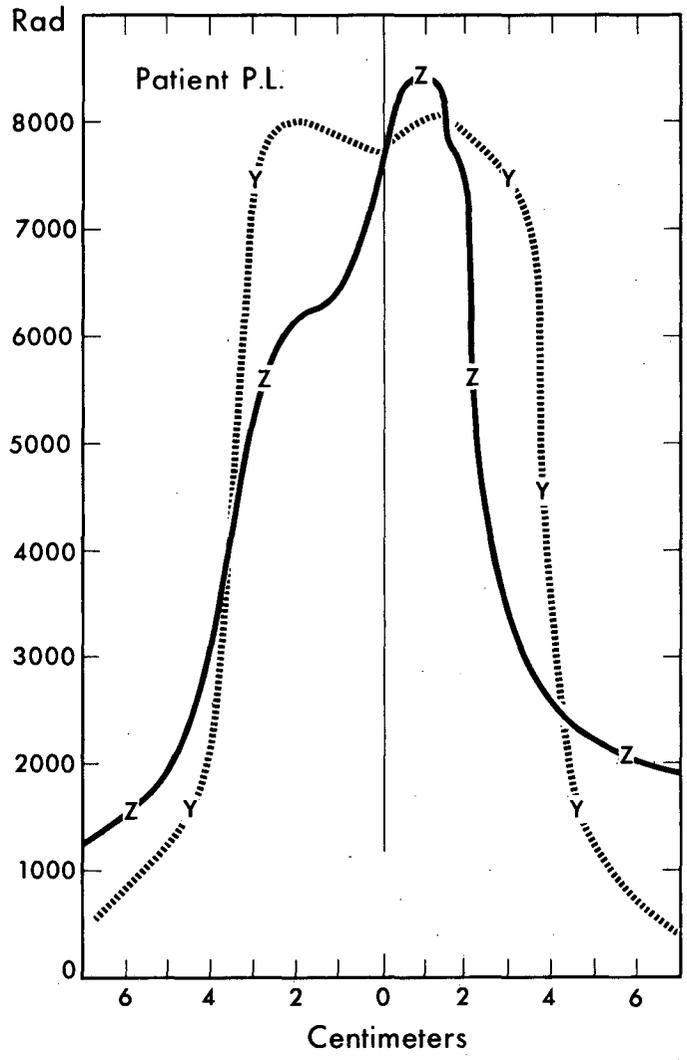
The first is that of a 43-year-old female with disseminated breast cancer, who received alpha-particle pituitary irradiation in 1958. The patient had a good remission, but in 1959 a lesion appeared in the right deltoid muscle. In 1960 we decided to treat this local lesion with radiation and to use the alpha-particle beam modified to make use of the Bragg effect. A total of 2,500 rad was given in 5 treatments over a 7-day interval. The beam was so modified that the maximum dose was delivered under the skin, and almost no dose went farther than 2.2 cm beneath the skin, a point still about 1/2 cm from the surface of the bone. The skin dose was about one-third the tumor dose, the major part of the dose going to the tumor itself. Therapy was well tolerated, and three months later the lesion was only a slightly depressed, slightly indurated area that was non-tender and showed no definite mass. There had been no skin reaction. Impairment of vision was noted several months later, and the presence of a bony metastatic lesion involving the left optic nerve beyond the optic chiasm was suspected. The patient was referred for neurosurgical exploratory craniotomy. At operation the left nerve was flattened and somewhat avascular. The left medial aspect of the optic nerve was biopsied, and the histologic changes were compatible with radiation damage. There was virtually complete demyelination with diffuse reactive proliferation of astrocytes and glial fibers and an increase in collagen in the sheath and interstitial tissue of the nerve. The radiation damage was probably due to an unusual anatomical location of the nerve with reference to the sella. The patient recovered from the operation uneventfully but subsequently had essentially no vision in the left eye. Vision in the right eye remained normal. Early in 1961 there

was evidence of slow, definite progression of her disease including probable liver involvement, and a trial of Halotestin was recommended. Shortly thereafter she developed acute pneumococcal meningitis and died 37 months following pituitary irradiation. At postmortem the sellar floor was found to have been punctured at the time of surgical removal of the hypophyseal remnants, which accounted for the subsequent meningitis.

The second case is that of a 4-year-old boy who, on each of three occasions at 3 month intervals in 1961, had undergone surgical excision of a lemon-sized brain tumor. After the last operation he was referred to us with a pathology diagnosis of recurrent parasagittal oligodendroglioma with signs of bilateral involvement of the motor cortex. We gave the patient alpha-particle radiation to the tumor through 13 fields in 8 treatments over the 23-day interval, the total dose being 8,500 rad in each case using the Bragg curve. Six months later there was no clinical evidence of tumor recurrence.

Figures 3, 4, 5 and 6 show the dosimetry to the tumor and the skin demonstrating the skin-sparing effect of the Bragg curve, there being 5,000 to 8,500 rad (each rad has an RBE on tumor of approximately 1.5) over the tumor with less than 2,000 rad to any of the skin areas.

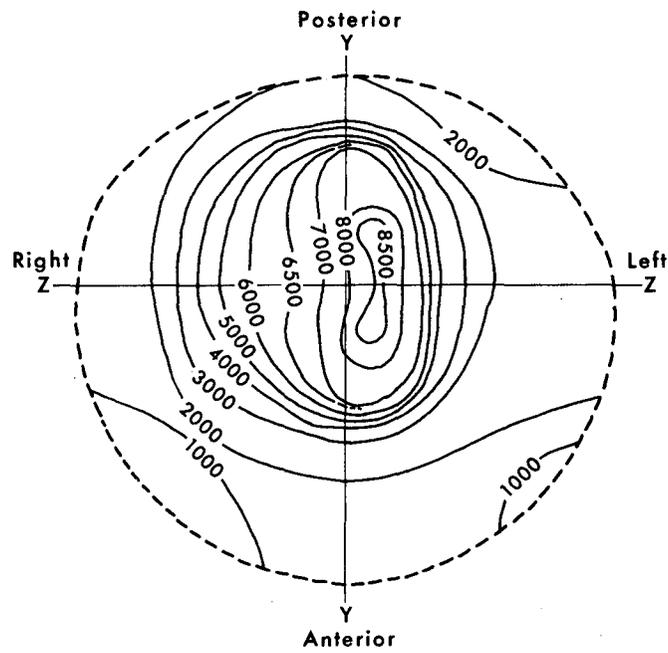
In conclusion, by using rotation techniques or the Bragg curve we find it possible to deliver enormous amounts of energy to localized areas of the body including the brain, the pituitary gland and the soft tissues. These studies, extending over a period of many years, provide background information on the long-term effects on the brain of relatively large doses of radiation. Recent studies, in which we have quantitated the effects of varying densities of ionization on an ascites tumor, have confirmed our previous findings in a mammary carcinoma, a lymphoma and a



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Fig. 3. Dose profiles along lateral axis ZZ and anterior-posterior axis YY.

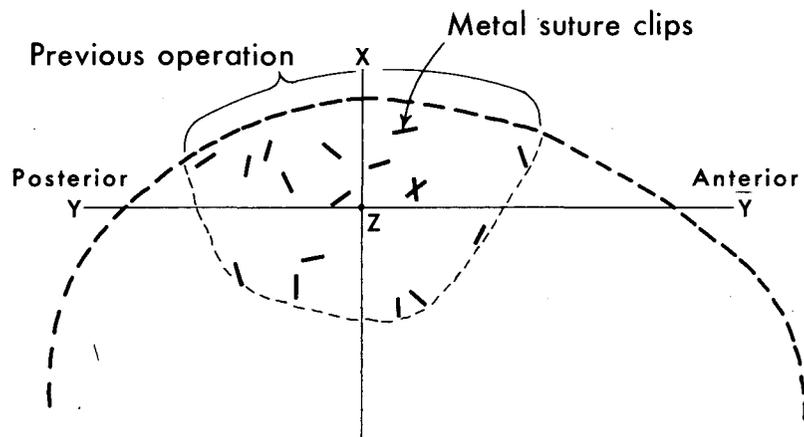
900 Mev alpha particles  
13 fields in 8 treatments  
23 days



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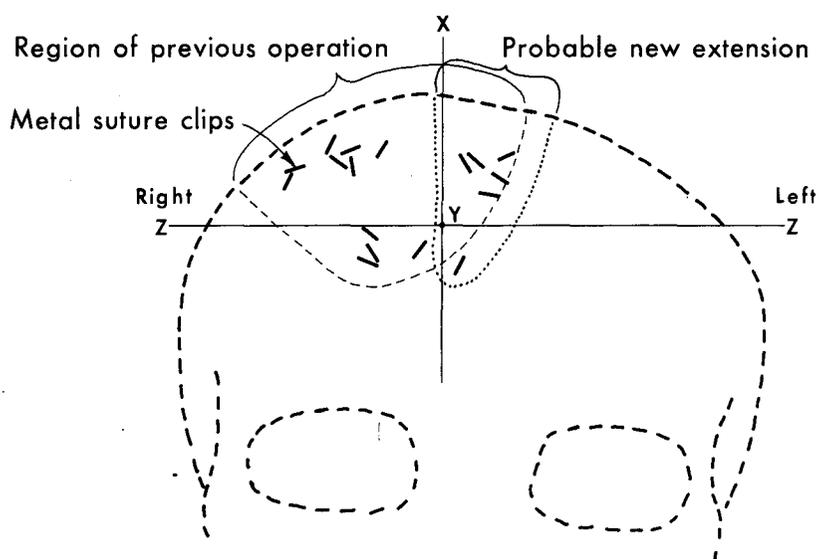
Fig. 4. Approximate isodose distribution in YZ plane.

Patient P.L.



MU-26743

Fig. 5. Lateral contour of skull, showing clips placed at previous operation.



Patient P.L.  
Dec 61 - Jan 62

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Fig. 6. Contour of skull showing location of tumor from operation clips in place.

lymphosarcoma -- that the Bragg curve of 910 Mev alpha particles has a greater RBE than the plateau region of ionization, indicating that each rad delivered at the depths, has the additional advantage of a greater RBE. Another possible advantage of these particles in therapy is their relative insensitivity to the oxygen effect; thus the relative anoxia in neoplastic tissues is not an adverse factor. These radiosurgically-induced effects open a wide field of therapy for patients with cancer, neurologic conditions such as kinetic disease and brain tumors, as further evidenced by the work of Doctors Leksell, Larsson, Naeslund and their associates in Sweden, <sup>16, 17, 18, 19</sup> and by Doctors Kjellberg, Sweet and Preston in the United States presented at this meeting.

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