HEAVY-PARTICLE IRRADIATION IN NEOPLASTIC AND NEUROLOGIC DISEASE*

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It is 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 fine 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.

Our work in this field began in 1935 when we studied the biological effects of heavy-particle radiation in normal and in neoplastic tissues and discovered the greater biologic effectiveness of these heavy particles (LET 18 to 20 kev/μ) at that time.1,8 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 of the dose and great scatter of these neutrons.10–17 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 roentgen 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.14

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

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† In these studies we had the valuable assistance of Mr. James Vale in charge of the cyclotron, John Lyman and Jerry Howard for measurement of doses, Wade Pratt who expertly made the plastic head masks, and Drs. Paul Toch, John Green, Lester Lawrence, Robert Weyand, Franco Sangalli, Richard Carlson, Peter Forsham and Michael Hogan who gave us valuable neurosurgical and radiological consultation.
TABLE 1
Classification of patients

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer of breast</td>
<td>146</td>
</tr>
<tr>
<td>Diabetes mellitus with retinopathy</td>
<td>57</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>20</td>
</tr>
<tr>
<td>Cancer of prostate</td>
<td>3</td>
</tr>
<tr>
<td>Chromophobe adenoma</td>
<td>2</td>
</tr>
<tr>
<td>Malignant exophthalmos</td>
<td>2</td>
</tr>
<tr>
<td>Other diseases, including brain tumors and</td>
<td>7</td>
</tr>
<tr>
<td>soft-tissue carcinoma treated directly</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>237</td>
</tr>
</tbody>
</table>

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.\(^{18}\) And, because the pituitary gland can be located accurately, 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.\(^{7,10,19}\) The classification of patients is listed in Table I.

There are 237 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.\(^{7,11,20}\)

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 outputs of various target-organ hormones revealed by thyroid iodine\(^{131}\) uptake, urinary estrogens, steroids and gonadotropins (Fig. 1).

In addition, the objectively judged regression in carcinoma of the breast approximates that following surgical removal of the pituitary gland. Some of the patients have done quite well. For example: 1 patient lived 5 years, 9 months after irradiation; 2 are still living 4 years after therapy; 4 survived 3 years (3 are still living); 5 survived 2 years (1 is still living); 21 survived 1 year (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 periods of time 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 treated thus far 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

\[\text{Median, percentage of preirradiation value} \]

\[\text{ESTROGEN (14.7 mg/24 h, N=29)}\]

\[\text{17-KETOSTEROID (9.3 mg/24 h, N=96)}\]

\[\text{I\textsuperscript{31}UPTAKE (22.1 mg, N=99)}\]

\[\text{FSH (+20, -10, N=108)}\]

\[\text{Months after irradiation} \]

\[\text{Fig. 1. Effect of pituitary irradiation, showing changes in estrogen, 17-ketosteroid, iodine\textsuperscript{131} uptake, and urinary gonadotropin values for patients with metastatic carcinoma of the breast.} \]

* Of the 10 deceased diabetics all had nephropathy and/or cardiovascular disease initially; 5 of these died of uremic complications and 3 of acute myocardial infarction.
complications, and we expect more encouraging results.

We have treated 20 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. 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 roentgen radiation were given doses in the range of 2,000 to 4,000 rad over a period of 1 month. The danger of damage to the cranial nerves and brain 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 radioinsensitivity of the pituitary gland to the techniques of irradiation then available; but now, with such high-energy particulate radiation as 900-million-volt alpha particles, much greater doses can be given safely. Of the 19 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 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.*

Similarly, urinary estrogens, gonadotropins, 17-ketosteroids and 20, 21-ketols, as well as iodine uptake and serum phosphorus were found to be 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 may result in extension of life and better control of acromegaly by heavy-particle pituitary irradiation.

Some neurological complications have resulted in patients who have received relatively large doses of radiation, especially in patients with advanced cancer of the breast. Of these patients, 6 had serious damage to the cranial nerves. Five had temporal-lobe damage resulting in temporal-lobe seizures, which were controlled easily with anticonvulsant 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 cancer of the breast coming to postmortem examination is now in preparation. However, during the past few years, since we began giving total dosages of 9,000 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.

Fig. 2 shows pre- and postirradiation 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 2 years after irradiation, and the patient remains well 3 years postirradiation.

* Professor C. H. Li, personal communication.
As examples of the use of the Bragg curve the following cases are presented.

Case 1. A 48-year-old female with disseminated cancer of the breast received alpha-particle pituitary irradiation in 1958. The patient had a good remission, but in 1959 there was activation and 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 so as 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 0.5 cm. from the surface of the bone. The dose to the skin was about one-third the dose to the tumor, the major part of the dose going to the tumor itself. Therapy was well tolerated, and 3 months later the lesion was only a slightly depressed, slightly indurated area that was nontender and showed no definite mass. There had been no reaction of the skin.

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 histological changes were compatible with damage from radiation. 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 damage from radiation probably was caused by 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 involvement of the liver, and a trial of Halotestin was recommended. Shortly thereafter acute pneumococcal meningitis developed and she died 37 months following pituitary irradiation. Post mortem the floor of the sella was found to have been punctured at the time of surgical removal of the hypophyseal remnants, which accounted for the subsequent meningitis.

Case 2. A 4-year-old boy, 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 pathologic 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, the total dose being 8,500 rad over the 23-day interval, in each case using the Bragg curve. Six months later there was no clinical evidence of recurrent tumor.

Figs. 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 8,000 rad (each rad has an RBE on tumor of approximately 1.5) over the tumor with less than 2,000 rad to any area of the skin.

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 case of mammary carci-

![Fig. 3. Case 2. Dose profiles along lateral axis ZZ and anterior-posterior axis YY.](image-url)
oma, a lymphoma and a 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 effect of oxygen; thus, the relative anoxia in neoplastic tissue 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 evidenced further by the work of Doctors Leksell, Larsson, Naeslund and their associates in Sweden,4-6.13 and by Doctors Kjellberg, Sweet and Preston in the United States presented at this meeting.

REFERENCES


