ALPHA AND PROTON HEAVY PARTICLES AND THE BRAGG PEAK IN THERAPY

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Two years ago we presented studies on the use of high-energy proton and alpha-particle beams in the treatment of 17 patients with acromegaly.[1] Today this work will be brought up-to-date, and then our work in treating patients with advanced diabetic retinopathy, Cushing's disease, and other conditions will be discussed.

Our interest in this subject began in 1935, when we first saw Wilson cloud-chamber pictures of the dense ionization produced in tissue by heavy particles (neutrons). This led us to investigate their biologic effects on normal tissue,[2, 3] and it was found that, per unit of ionization produced in tissue, these particles were several times as destructive as equal doses of conventional X rays or gamma rays. Immediately safety standards were set up, the permissible exposure for personnel working around cyclotrons and other neutron sources being set at one-tenth that allowed for X rays or gamma rays.

We then investigated the biologic effects of heavy particles on neoplastic tissue, and found that there was possibly an even greater effect than that on normal tissue.[4, 5] This led to the trial of neutron beams in the treatment of cancer.[6] These first efforts, however, were disappointing because of the great scatter and lack of penetration of these relatively low-energy neutrons.

During the war years accelerator theory and practice advanced, and cyclotrons were soon developed which were capable of producing heavy particles with much greater energies.[7] These heavy, charged particles had greater penetration, less scatter, and they also produced very dense ionization (like we had observed in our earlier neutron studies) at the end of their track in tissue (Bragg peak effect).[8] A recent investigation of the relative biological effect (RBE) of Bragg peak ionization in two different ascites tumors in mice, studied *in vivo*, demonstrated the findings we had expected on the basis of our earlier neutron experiences. The results showed that the RBE per rad at the Bragg peak of 900 MeV alpha particles is

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greater than that of X rays.[9] It is also of interest to point out that the particles with higher linear energy transfer (LET) are less sensitive to the "oxygen effect", a possible important factor in the treatment of neoplasms which are usually relatively anoxic.[9, 10, 11]

Heavy particles with great penetration, little scatter, the Bragg peak effect, and lack of "oxygen effect", give the biologist and physician a method for delivering radiation deep within the body with greater biological effect per rad as well as greater depth-dose than skin-dose. Thus it is possible to deliver doses of radiation to selected areas in the body—much larger doses than can be delivered with conventional radiations such as X rays or gamma rays. Furthermore, when the Bragg peak is used, each unit of dose delivered has a relatively greater effect, and each dose is less effected by the decrease of tissue oxygenation.

In 1948 Bragg peak irradiation was directed to neoplasms in animals and it was shown that one could pass the beam through the animal's body and destroy a tumor situated on the opposite side at the position of the Bragg peak.[12] During the past 10 years we have treated over 300 human patients with heavy-particle irradiation, using the rotation technique with or without the Bragg peak, to suppress pituitary function, to treat tumors directly, or to produce lesions in the nervous system.[13, 14, 15, 16, 17]

During the past two years, since speaking to this Association, we have treated 9 additional acromegaly patients, bringing the total to 26. There have been no additional deaths—the one patient who had died was a patient with long-standing acromegaly and cardiomegaly who suffered a coronary occlusion 3½ years after treatment. Thus, twenty-five patients of the treated group are living, 6 of them having been treated over 5 years ago. Six patients have been treated too recently for follow-up evaluation, but the other patients continue to demonstrate beneficial effects, both subjectively and objectively. It is usually assumed that any changes in the typical coarse acromegalic facies of these patients would occur primarily in the soft-tissue mass, but after heavy particles, skeletal alterations were also detected on comparison of roentgenograms of the hands and feet. These showed a decreased thickness of the cortical bone. There were also associated changes in calcium turnover as measured with calcium 47.

An interesting finding was the improvement in the glucose metabolism, demonstrating that heavy particles delivered to the pituitary gland influenced this metabolic function. In our last report we mentioned that three of the acromegalic patients who had associated diabetes requiring treatment were able to discontinue their anti-diabetic therapy following pituitary irradiation, and with good control of their diabetes. We have since evaluated the glucose tolerance curves of 9 additional patients who, while

not frankly diabetic, demonstrated abnormal curves prior to therapy. Following therapy their curves were improved: the six patients who were over two years post-irradiation showed normal glucose tolerance curves; the other three who were only 7 to 10 months post-irradiation had curves which were improved but still abnormal. We observed no changes in the glucose tolerance curves of those patients who had normal curves prior to heavy-particle administration.

More than ninety patients with severe advanced diabetic retinopathy have now been treated with 900 MeV alpha particles to achieve partial or complete hypophysectomy in an attempt to slow down the progressive, severe retinopathy and to prevent blindness.[17] The insulin requirements of these patients fell after therapy. Retinal photographs were taken before, and periodically after, therapy for evaluation of retinal changes. Re-evaluation of the retinopathy was done for seventy-nine patients who had been followed for a sufficient time, and over fifty per cent of these patients had been helped. Twenty-nine showed stabilization of their vision and retinopathy, and an additional 18 patients showed improvement in vision and retinopathy. The improvement was associated with fewer hemorrhages and microaneurysms, and with less exudate.

Five patients with Cushing's disease, in which metabolic studies indicated that the anterior pituitary gland should be attacked, have received heavy particles to the pituitary gland. Two have just completed therapy. The other three have all shown marked improvement with disappearance of the Cushingoid features and a return to normal of the metabolic abnormalities.[15] The first patient was treated over 4½ years ago, and her remission continues to date.

In addition, we are using the Bragg peak for direct tumor irradiation in patients with brain and other tumors.[16] The problem of locating the borders of the tumor so that the Bragg peak can be placed correctly still must be solved.[18]

We are continuing to enlarge our series of patients in the several categories. These heavy-particle beams are not only being used for hypophysectomy and direct tumor irradiation, but also to produce lesions in the nervous system for the relief of symptoms in patients with Parkinson's disease. Heavy-particle therapy is also being administered by Kjellberg and associates[19, 20] at Harvard University, and by Larsson, Leksell and co-workers[21, 22] at the University of Uppsala. In addition, the possible use of pi mesons in therapy[23, 24, 25] is being investigated. Heavy particles are generated by pi mesons when directed to tissue and thus dense ionization is produced at the end of their path. Their interesting physical characteristics are currently being studied by Richman *et al.* in our laboratory.[25]

In conclusion, there are today cyclotrons and accelerators available

in many places throughout the world which are capable of delivering high-energy, heavy particles,[26, 27] and it is hoped that other groups will soon undertake their use in investigation and in therapy.

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DISCUSSION

DR. EDWARD ROSE, (Philadelphia): I would like to ask Dr. Lawrence about the results in his patients with malignant exophthalmos. Is he in position to evaluate results? And also, what are the dose factors he employed in the treatment of the patients with Cushing's disease?

DR. LAWRENCE: In the case of this so-called malignant exophthalmos, we had the advice of many good men in the country on this question, and we have treated three cases. The first one, treated about seven years ago, had a Naffziger operation six weeks later, and so we could not evaluate the end results. The second patient was treated about four years ago, and we achieved an excellent result. This lady had a very serious malignant exophthalmos. The third patient was treated too recently for assessment of results.

However, we have had several patients referred to us since then, and we have turned them all down. This is an area in which one cannot quite be sure that the

pituitary is at fault. I would be very much interested in Dr. Rose's comments, because there are so many other factors that may be related to this problem.

The dose we are giving in Cushing's disease, actually a pretty high dose, is from 6,000 to 11,000 rads in 11 days and 6 sittings. Because of our long experience of over 10 years using heavy particles, we know our doses are much below that endangering the structures surrounding the pituitary. However, we think Cushing's syndrome is a pretty serious disease and, if we can get agreement that the individual patient is not a case for exploration of the adrenals, we think that this risk, if there is any, is really very small.