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21 YEARS EXPERIENCE IN THE TREATMENT OF ACROMEGALY
CUSHING'S DISEASE AND NELSON'S SYNDROME

Presented at the Pacific Interurban Clinical Club, Vancouver, B.C. Canada,
October 5 - 6, 1978.

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INTRODUCTION

Since 1957, we have an intensive experience in the study, diagnosis and treatment of these three syndromes. The present report will emphasize the long-term results chiefly, since previous reports have given in detail the methods used, the physical aspects and dosimetry of the radiation and many detailed metabolic studies. (1)(2)(3)(4)(5)(6)(7)(8)(9)(10) These conditions in the past have been treated chiefly by surgery or conventional pituitary radiation or both, whereas in our work, heavy particle radiation - plateau or Bragg Peak have been used, administered with the aid of a stereo tactic set up to hold firmly the patient's head, and by head and body rotation, to limit to safe levels that amount of radiation delivered to the cranial nerves and temporal lobes.

One of us had his first experience with tumors of the pituitary gland as an intern at the Peter Bent Brigham Hospital under Dr. Harvey Cushing. (12)(13)(14)(15) At that time, patients with pituitary tumors were being referred to him from all over the world and the wards were literally full of such patients, especially acromegalic tumors and chromophobe adenomas. It was during that period of time that the so-called Cushing's disease was not recognized and as a surgical intern on Dr. Cushing's service there was a patient admitted with a diagnosis of pluriglandular syndrome and it was one of our jobs to work this patient up and present it on rounds to Dr. Cushing. He then for

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the first time made the diagnosis of basophilic adenoma of the pituitary gland as the cause of the syndrome. Since then the syndrome has been known as Cushing's disease. It was not long before other patients with this clinical picture were being seen at the Brigham and later on when one of us was on the faculty of the Yale Medical School where Dr. Cushing was professor of the history of medicine. Many patients with Cushing's disease were being referred to him and we took part in their study and treatment. The treatment at that time was pituitary radiation first carried out by Dr. Merrill Sisman, the radiologist at the Brigham Hospital. However, the doses given were insufficient.⁽¹⁶⁾ In the case of the first patient at the Brigham, diagnosed as having a large basophilic adenoma, several years later the patient died and a post-mortem showed a large basophilic adenoma of the pituitary. In the intervening years, you will remember, and even today many patients with Cushing's disease were treated by bilateral adrenalectomy. But in recent years it has become recognized that the primary defect is either in the pituitary itself or in the hypothalamic adrenal axis and the point of attack should be the pituitary gland. In relatively very recent years with the transphenoidal pituitary operation being re-discovered, although it was used by Cushing on some patients, more and more patients with Cushing's disease are being treated by hypophysectomy - either removing a micro-adenoma or a macro-adenoma.⁽¹⁷⁾ However, there has not been adequate follow-up time on any large series of such patients treated by surgery so that one could analyze the long-term effects with reference to the return of the metabolic findings to normal and the relief of the clinical symptoms and signs. It will be another 5 or more years before such a series will be followed long enough

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for comparison with our series.

Since 1957 we have seen 796 patients with pituitary tumors but today we will be talking about 429 of these patients, these patients having hormonal hyper-secreting tumors. As stated we have used in treating these patients a beam of alpha particles or protons using a stereotactic method for alignment of the pituitary sella and delivering to the pituitary doses something like twice that delivered by the usual photon method. (Fig.1) In this way we have observed rather remarkable results. The method consists of rotation of the head right and left through angles of 30 degrees and continuous body rotation. Thus one is able to deliver to the pituitary a much larger dose than is possible with photons without damage to the nervous tissue such as the third nerve, other cranial nerves and the temporal lobes. Approximately 10% of the dose may reach the third nerve; consequently in the computerized setting of the dosage schedule for each patient it is calculated to give less than 2800 R to the third nerve. In some patients, especially in the early work, we used the so-called Bragg Peak. (18) Also we treated a few patients who had received previous photon radiation but since 1961 this has been discontinued and we no longer treat any patients who had previous radiation therapy and we do not use the Bragg Peak because of the difficulty of exact alignment. Recent work, however, with another new beam of much heavier particles such as carbon-12 or neon and a method of so-called autoradio activity localization for the location of the peak, it will be possible to give larger doses than now given⁽⁴⁾. This will be especially important in the case of Cushing's disease, where most patients are not given as much radiation as one would like to give. Consequently in the early months after radiation we

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give them drug therapy until the radiation effect has taken place.

The criteria for selection of our patients is that described by Hardy. A grade 1 tumor is less than 10 mm in size, grade 2 has an enlarged sella or a suprasellar extension with type A being moderate to massive, and B and C involvement of the optic chiasm and/or the third ventricle. Grades 3 and 4 are the most common in our series of patients, that is, a rather massive enlargement of the sella turcica. We have found by using all available methods for visualization of the sella turcica that the most reliable method is pneumoencephalography. All patients who are treated by the beam have such a study to avoid patients with suprasellar extension or massive sphenoid extension; however, we do treat patients who have sphenoid extension where we can appropriately place the beam.

The goals of the treatment, of course, are return of the patient's symptoms and signs in the direction of normal or to normal and the return of the metabolic findings to normal.

In acromegaly as will be pointed out in Figure 2, many of the patients - actually 65 in our present series - had had prior surgery. Sixty-five out of 299 patients had had prior surgery, usually transphenoidal which was unsuccessful. Figure 3 demonstrates the fall in growth hormone, and Figure 4 the survival in years after therapy (median 16 years). One should mention that as a group these patients have often been refused surgery because of the various factors and in general are non-selected by us, if the beam can be placed accurately. If not, we of course then refer such patients to the surgeon. In the early part of our work, prior to 1961 we did have rare neurological complications (Table 1) but since then less than 1% of the patients have had any neurological complications. Fig. 5 indicates the delay

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before patients are referred for treatment. Finally Fig. 6 summarizes a group of patients with acromegaly, who received prior unsuccessful therapy. They were then given heavy particles followed by the return of the growth hormone to normal in most cases.

NELSON'S SYNDROME

Possible addition re. incidence of Nelson's syndrome:

Pituitary tumors have developed in about ten percent of patients with Cushing's disease associated with adrenocortical hyperplasia who had been treated initially with total adrenalectomy according to reports of several authors (19,20,21,22,23,24,25,26). They expressed concern that adrenalectomy may serve as a triggering mechanism (lack of feed back) responsible for the clinical appearance and rapid growth of the pituitary tumors. Orth and Liddle (5) reported that none of the nineteen patients treated first by pituitary irradiation and later by bilateral adrenalectomy had developed evidence of pituitary tumors during a follow-up period of one to thirteen years, and they pointed out the possibility that patients who had received pituitary irradiation prior to total adrenalectomy are less likely to develop large pituitary tumors. However, Wild, Nicolis and Gabilove (8) cited two of their patients who had initially undergone unilateral adrenalectomy and pituitary irradiation (conventional radiotherapy) who subsequently required total adrenalectomy to control their disease and then later developed skin pigmentation and pituitary tumors. They concluded that experience to date indicates pituitary irradiation may reduce the incidence of Nelson's syndrome, but that its effectiveness has not been precisely established. We also have observed Nelson's syndrome in two instances after treatment of our patients with Cushing's disease.

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There are fifteen patients in this group (Fig. 5) None of them was treated previously by our method of treatment. Six had prior unsuccessful surgery and there is one death due to an invasive tumor, which is not uncommon in these MSM secreting tumors. There were no other complications.

PROLACTIN TUMORS

We have had limited experience in the treatment of prolactin secreting tumors (29 patients). Nine of these had previously had unsuccessful surgery. Twenty-four patients had sellar volumes less than 1100 cu. mm. in size known as a micro adenoma, the others were Grades 2, 3 and 4 with relatively large sella turcica. With reference to replacement 10% of those patients required adrenal cortisone replacement and a lesser number replacement with thyroid or gonadal replacement. Approximately one third of patients we have treated for acromegaly have ultimately required replacement therapy.

The most important message that we would like to leave you gentlemen today is that in order to compare the various methods of therapy for pituitary tumors, it is especially important that literally hundreds of patients be followed for many years after treatment. It will require a good many years before the surgical end results can be compared with our results. We emphasize in the case of acromegaly the median survival is something better than 16 years and this will improve with the passage of time.

In closing, it is important to point out that we do not turn patients away with many of them having been previously turned away as poor surgical risks. As a group, our patients are a poorer group to treat than the average surgically treated patient. You will note also in Figure (6) that patients with acromegaly are treated approximately 8 years after the diagnosis has been made. If the diagnosis is made earlier and treatment administered

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it seems that survival may well approach nearer normal.

The causes of death in acromegaly are primarily due to vascular disease. It is also to be noted that approximately 1/3 of the patients with acromegaly have hypertension and about 1/3 of these have a return of blood pressure to normal and about 1/3 to the direction of normal. The mechanisms of the etiology of hypertension in these patients is under intensive study in our laboratory, but it is not understood yet. Advance cardiomegaliacs of which we have 5 or 6 do not have the return of their heart to normal size.

Fig. 7 provides a summary of all patients treated up to Sept. 1977 and Fig. 8 lists cyclotrons and synchrotrons which are being used or could be used as described in the paper.

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