

THE ALPHA PARTICLE OR PROTON BEAM IN RADIOSURGERY OF THE PITUITARY GLAND FOR CUSHING'S DISEASE*

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focused on Cushing's Disease

In the early days of the modern nuclear era, one of the first studies carried out as a means of assessing the danger from some of the radiations from the nuclear age was on the biologic effects of neutron rays. These neutral heavy particles, having the approximate weight of a proton, are approximately two thousand times as heavy as electrons and are called heavy for this reason. The early workers around the cyclotron were being constantly bombarded by these particles in addition to gamma rays, and they asked themselves, "What would be the safe daily dose?" For this reason it was extremely important to study the biologic effects of these heavy particles as a means of predicting damage to workers, and thereafter to set safety standards and thus to avoid the history of radiation damage seen in the early workers with radium and x-rays. Our first studies in 1935 were to compare standard 200-kv x-rays with neutron rays, using as test objects the whole bodies of mice and rats and transplantable forms of cancer in mice.^{1,2} It was found early that neutrons had a biologic effect several times greater than equal doses of x-rays, and appropriate safety standards were set up. Also at that time there was some indication that there might be a favorable differential effect of neutron rays over x-rays on tumor tissue as compared to normal tissue — that is, a relatively greater effect on neoplastic tissues. These early experiments, therefore, suggested that neutrons might have value in the therapy of cancer. Consequently, a study was carried out on advanced cancer, but the results were disappointing largely owing to the fact that these neutron rays had poor penetration and great scatter.^{3,4} In 1945, when heavily-charged particles with higher energies became available with the development of the increasingly larger accelerators, it seemed important to investigate heavy particles further since these high-energy particles had, in addition to the previously observed greater biologic effect at the Bragg peak, great penetration and little scatter,⁵⁻⁷ and in the intervening years such studies have been carried out on both animals and man. When the so-called Bragg peak of these high-energy, heavy-charged particles is used in the delivery

of radiation energy to various tissues one could predict that, like the early neutron studies, a greater biologic effect per unit of ionization would result,^{6,8,9} and with the added properties of greater penetration and little scatter, it is possible to produce localized lesions in the tissue and nervous system with little damage to surrounding structures.¹⁰ In 1954 we set out upon a study in clinical medicine in which these high-energy protons and alpha particles have been used in various forms of so-called "bloodless" surgery, or radiosurgery. This has led to their use in the direct treatment of tumors and the suppression or ablation of the function of the pituitary gland in such conditions as advanced breast cancer, diabetic retinopathy, malignant exophthalmos and acromegaly.¹¹⁻¹⁷ They have also been used in the production of lesions in the thalamic nuclei in the treatment of kinetic disease.^{18,19} This report deals with our experience in treating Cushing's disease.

Pituitary basophilism, or Cushing's disease, first described by Harvey Cushing²⁰ in 1932, can now be explained on the basis of excessive hormonal secretion by the adrenal cortex. Cushing's early interpretations of the symptomatology and physical, laboratory and pathological findings led him to relate the condition to either hyperplasia or adenoma of the basophilic cells of the anterior lobe of the hypophysis. Typical of the early cases was that reported by one of us in 1935 during work with Dr. Cushing.²¹ We found a small basophilic pituitary adenoma associated with bilateral adrenocortical hyperplasia and adenomas and a parathyroid adenoma. In those early days therapy initially was directed toward the pituitary gland. However, partial surgical procedures and orthovoltage x-ray therapy were only irregularly associated with adequate and sustained remissions,^{22,23} and, furthermore, diffuse basophilic hyperplasia or adenomas of the pituitary gland were infrequently found. In the ensuing years there has been a tendency to attribute the syndrome to pituitary-adrenocortical hyperplasia, and, with the advent of adrenocortical steroids, total or nearly total adrenalectomy became the treatment of choice.^{24,25} However, the recognition of pituitary tumors in patients after adrenalectomies for adrenal hyperplasia^{26,27} and the development of more effective methods of studying adrenal hyperfunction²⁸ have indicated that the primary disturbance is frequently due to excessive ACTH secretion by the anterior pituitary gland in line with Cushing's early thinking.²⁹

In spite of great progress in the knowledge of the chemistry and physiologic function of the pituitary hormones no truly satisfactory pharmacologic method

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of suppressing pituitary function has yet been developed. Treatment of pituitary hyperfunction and tumors has been limited to surgery, x-rays or gamma rays. A review of the results in cases treated with pituitary irradiation shows that a higher incidence of permanent and satisfactory remissions has been associated with the administration of larger doses of irradiation.^{30,31} Unfortunately, the use of conventional x-rays or gamma rays has been limited by the dose (2000 to 3000 r) that can safely be delivered to the sella turcica.³² Because of relatively great scatter and low biologic effectiveness, doses of adequate depth cannot be attained with these radiations without endangering the surrounding structures such as the cranial nerves, hypothalamus and temporal lobes. Heavy particles, however, with the advantageous properties mentioned above, offer a method of suppressing pituitary function and alleviating the symptoms and signs of Cushing's disease, and this paper describes and discusses the use of 900-mev alpha particles for this purpose.

CASE REPORTS

CASE 1. R.K., a 37-year-old housewife, was referred to the Donner Laboratory in April, 1959, because of bilateral adrenal hyperplasia. In the spring of 1957 she began to gain weight, and during the next 18 months her weight increased from 52.6 to 67.6 kg. (116 to 149 pounds). By January, 1958, she complained of weakness and lethargy and was observed to have mild hypertension. During the next few months amenorrhea, hirsutism and backache developed. Since 1957 she had been quite emotionally unstable.

Physical examination showed an obese woman with rounding and plethora of the face and a prominent cervicodorsal fat pad. There was a fine hair growth over the face and trunk but no pigmented striae. The blood pressure was 140/100.

Preliminary laboratory studies revealed a slight lymphopenia and a diabetic glucose tolerance curve. The hemoglobin was 13.5 gm. per 100 ml. The serum calcium, phosphorus, creatinine and electrolytes were normal. X-ray examination showed demineralization of the lumbar and dorsal spine; the sella turcica was not enlarged. The basal excretion of urinary 17-hydroxycorticosteroids was 16.5 mg. per day, and this increased to 58.6 mg. per day after an 8-hour infusion of ACTH (20 units). A threefold increase in urinary 17-hydroxycorticosteroids was observed after a 4-hour infusion (30 mg. per kilogram of body weight) of metapirone.³³ The urinary 17-ketosteroids were also elevated. Adrenal steroid excretion was not suppressed by the administration of dexamethasone, 2 mg. per day for 3 days, but was suppressed when a dose of 8 mg. per day was similarly administered. The adrenal glands appeared normal on a presacral air study.

Studies repeated in our laboratory confirmed these findings, and, in addition, the 24-hour thyroid I¹³¹ uptake was 16 per cent, the protein-bound iodine was 3.9 microgm. per 100 ml., and the urinary gonadotropins were negative at 1:12.5 mouse uterine units.

Eighty-five hundred rad of 900-mev alpha particles were delivered to the pituitary gland over an 11-day interval ending on May 16. One month after irradiation the patient began to menstruate, having been amenorrheic for the preceding 15 months. There was little change in her other symptoms or appearance. The urinary 17-hydroxycorticosteroids remained elevated at 17.2 mg. per day; however, the 17-ketosteroids had fallen from 13.5 to 7.0 mg. per day (normal, 5 to 10 mg.). The urinary gonadotropins were now positive at 1:12.5 mouse uterine units.

To determine the histologic adrenal status, the left adrenal

gland was resected on August 14. Pathological examination showed nodular adrenal hyperplasia.

In November the patient was greatly improved. The menses were regular, and she was clinically euthyroid. She had lost 6.4 kg. (14 pounds) in weight and there was significant regression of the cushingoid features. The blood pressure was 130/80. The urinary 17-hydroxycorticosteroids had fallen to 10.1 mg. per day, and the exaggerated responses to ACTH and metapirone were no longer present (Fig. 1 and 2).

By January, 1960, her appearance was normal (Fig. 3). Over the next 2½ years she remained asymptomatic. The menstrual periods continued, and she was euthyroid. In October, 1962, the protein-bound iodine was 3.5 microgm. per 100 ml., and the thyroid I¹³¹ uptake 23 per cent. The urinary gonadotropins remained positive at 1:12.5 mouse uterine units. The 24-hour urinary 17-hydroxycorticosteroids were 9.5 mg.; the 17-ketosteroids were 5.7 mg. Urinary adrenal steroids did not increase after a 4-hour intravenous infusion of metapirone. The response to intravenously administered ACTH was normal.

CASE 2. J.R., a 32-year-old secretary, was referred to the Donner Laboratory in 1961 because of a "ballooned" sella turcica and hyperpigmentation. Although she had been overweight for many years she became progressively more obese since her 1st pregnancy in 1950. Subsequently, facial hair growth, acne, back pain and weakness developed, and she felt confused at times. In January, 1954, she was seen by a private physician because of headache and amenorrhea.

In July she was admitted to another hospital. Physical examination revealed truncal obesity, acne, plethora, hirsutism and pigmented striae. The blood pressure was 142/114. Pelvic examination was normal. The white-cell count was 10,000, predominantly neutrophils. The hemoglobin was 14 gm. per 100 ml. The fasting blood sugar and serum electrolytes were normal. The urinary excretion of 17-ketosteroids was 36 mg., and that of 17-hydroxycorticosteroids 18 mg. per 24 hours. A presacral air study suggested some enlargement of the left adrenal gland. Skull films were interpreted as showing a normal sella turcica. A diagnosis of Cushing's syndrome due to bilateral adrenal hyperplasia was made, and the left adrenal gland was totally excised, and the right subtotally. Microscopical examination of the adrenal glands revealed no prominent abnormality.

After operation the menses returned, and the other symptoms gradually improved. The patient was maintained on small doses of cortisone. In September, 1955, the urinary 17-ketosteroids were 5.6 mg. per 24 hours. She had lost 22.7 kg. (50 pounds) in weight and was normotensive. Subsequently, she was able to discontinue cortisone.

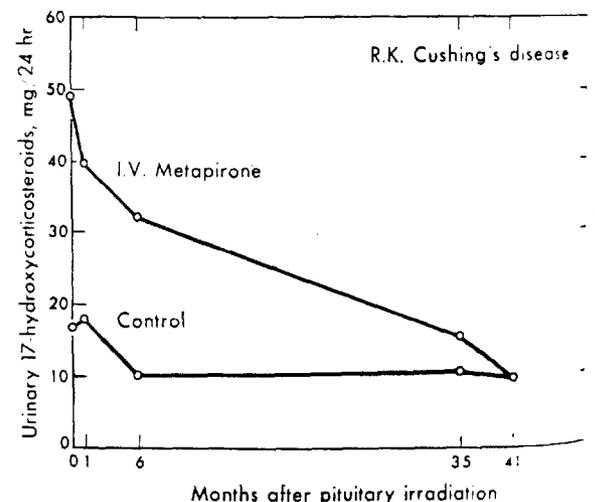


FIGURE 1. Serial Changes in the Response to Intravenous Metapirone in Patient R.K.

The Normal Ranges Are Represented by the Shaded Area.

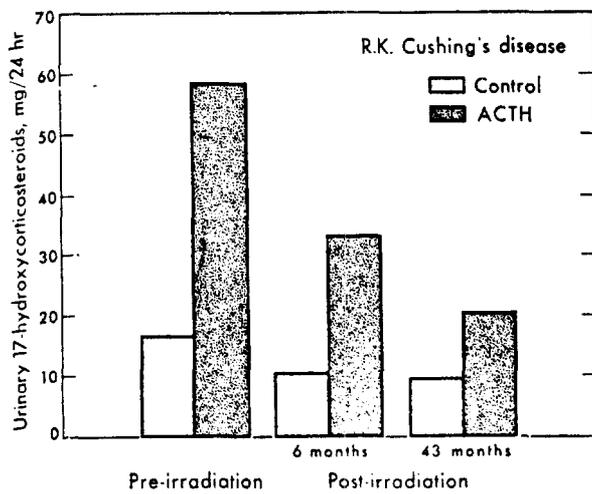


FIGURE 2. Intravenous ACTH Tests, Performed on Patient R.K., Showing the Characteristic Response Observed in Cushing's Disease before Treatment and Comparing the Changes That Occurred at Six Months and Forty-three Months after Treatment.

April, 1957, she had the florid features of hyperadrenocorticism again. In addition there was some pigmentation of the hands. The urinary 17-hydroxycorticosteroids were 20 mg., and the 17-ketosteroids 14 mg. per 24 hours. The sella turcica was somewhat deeper as compared to earlier x-ray studies of the skull, but considered normal. Her condition remained unchanged, and in November, 1957, the right adrenal remnant was removed. The pathological diagnosis was "regenerative nodular hyperplasia." She had a stormy postoperative course owing to multiple episodes of adrenal insufficiency, but was finally discharged on 37.5 mg. of cortisone and 0.125 microgm. of 9-alpha-fluorohydrocortisone per day.

After operation the symptoms of hyperadrenocorticism improved. She had numerous episodes of adrenal crisis usually associated with infection. She failed to return for follow-up study for several years and was not seen until August, 1961, when she was admitted to the hospital in adrenal crisis. She was diffusely pigmented. Although pigmentation of the hands had been noted in 1957, it was apparently first noticed by her in 1958, but did not become prominent until 1960 and had been gradually increasing. X-ray study of the skull showed further enlargement of the pituitary fossa, with erosion of the dorsum sellae and the floor of the fossa.

In September, 1961, the patient was admitted to Donner Pavilion. She had no complaints except for a rare headache and some menstrual irregularities. Physical examination revealed a pleasant, obese woman with generalized brownish pigmentation of the skin. The pigmentation was particularly prominent in the creases of the hands and over the elbows and knees. The blood pressure was 110/80. The remainder



FIGURE 3. Photographs Showing Patient R.K. before Pituitary Irradiation (Left), and Eight Months after Treatment (Right).

of the physical examination was unremarkable. The visual fields were normal. Laboratory studies revealed a normal hemogram. The fasting blood sugar was 73 mg., the protein-bound iodine 5.6 microgm., and the serum cholesterol, 228 mg. per 100 ml.; urinary gonadotropins were positive at 1:12.5 mouse uterine units. The basal excretion of urinary 17-ketosteroids was 1.9 mg., and that of 17-hydroxycorticosteroids 5.6 mg. per 24 hours on replacement therapy. ACTH stimulation did not produce any increase in steroid excretion. The plasma ACTH assay was 30 milliunits per 100 ml. This level was not altered by the administration of 2 mg. of dexamethasone for 3 days or by 8 mg. given for an additional 3 days. Serial review of previous skull films revealed that the area of the sella turcica measured 9 by 12 mm. in 1954, 12 by 13 mm. in 1957 and 15 by 16 mm. in October, 1961.

Five thousand rad of alpha particles were delivered to the pituitary gland over an 11-day interval ending on November 10, 1961. The treatment period was uneventful.

The patient was next seen in April, 1962. She continued to work as a secretary and was well except for several minor episodes of adrenal insufficiency associated with respiratory infections. The menses were normal. Physical examination was unchanged except that there appeared to be a little lessening of the pigmentation. The protein-bound iodine was 6.2 microgm. per 100 ml., and the I^{131} uptake 16 per cent in 24 hours. Urinary gonadotropins were negative at 1:12.5 mouse uterine units.

In October, 1962 (10 months after irradiation), there had been some definite lessening of the skin pigmentation. The menstrual periods had been somewhat irregular. She appeared euthyroid. The protein-bound iodine was 4.9 microgm. per 100 ml., and the I^{131} uptake 13 per cent. The pituitary fossa had not changed. The plasma ACTH level was less than 30 and greater than 2 milliunits per 100 ml.

DISCUSSION

These 2 cases illustrate most of the problems that are encountered in the management of patients with hyperadrenocorticism due to bilateral adrenal hyperplasia. Although complete adrenalectomy can produce a prompt remission of the symptoms of hyperadrenocorticism the surgery is not without risk, and the management of totally adrenalectomized patients is often difficult in spite of available replacement steroids. The appearance of pituitary tumors in many patients adrenalectomized for Cushing's disease is an additional problem associated with this form of therapy. Recent studies of pituitary and adrenal function,²⁸ as well as a more frequent recognition of pituitary tumors in patients with Cushing's disease, require that the pituitary gland be considered primarily in the treatment of many cases of bilateral adrenal hyperplasia. Recently, a number of cases have been successfully treated by surgical hypophysectomy³⁴ or by the implantation of radioactive sources such as Y^{90} or Au .^{19,35} The latter methods of radiation have been resorted to because previous experience with x-rays or gamma rays has not been entirely satisfactory. These types of therapy have been limited by the amount of radiation that can be delivered safely without damage to neighboring central-nervous-system structures. Prolonged remissions after x-ray or gamma-ray therapy have been infrequently observed, and partial response and relapse occur in at least 70 per cent of the patients so treated.^{28,36,37} The best results have

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often occurred only after several courses of radiation, these being seen in patients receiving the largest amount of x-rays or gamma rays.^{30,31,38,39} Surgical hypophysectomy and surgically implanted radiation have certain risks and side effects that it would be desirable to avoid. A method of adequately inhibiting anterior pituitary function by an externally delivered energy source would be the most suitable form of treatment. This can now be accomplished by the use of heavy particles, such as protons and alpha particles, which are imparted extremely high energies in the large accelerator and delivered to the sella turcica in desired amounts.

Case 1 received 8500 rad of alpha particles delivered to the pituitary gland in six treatments over an eleven-day period. Her remission has lasted for more than three years. One month after radiation the menses resumed. Other signs of pituitary-irradiation effect are evident in the less exaggerated response to intravenously administered metapirone (Fig. 1) and the fall in the excretion of the 17-ketosteroids. These changes occurred before adrenalectomy. Furthermore, the fact that there were progressive changes in the response to administration of ACTH (Fig. 2) and metapirone (Fig. 1) after adrenalectomy suggests that the exaggerated responsiveness of the residual adrenal gland was changing and that removal of the left adrenal gland was probably not of major importance. Serial observations of the changes in the response to metapirone appear to be helpful in determining the adequacy of pituitary suppression. It was of interest that in the study of the effects of intravenously administered metapirone and ACTH in one of our diabetic patients, who had had a unilateral adrenalectomy before being referred for pituitary irradiation for diabetic retinopathy, the responses were normal and uninfluenced by the absence of one adrenal gland. Remissions after unilateral adrenalectomy have been reported by Soffer et al.,³⁰ who observed better results when they combined unilateral adrenalectomy with x-rays given to the pituitary gland and believe that, although administration of the radiation promptly after removal of the adrenal gland was desirable, the clinical response was directly related to the amount of radiation.

It should be emphasized that although Case 1 received a relatively large amount of alpha-particle radiation, the only manifestations of altered pituitary function are the remission of the disease and a reduced "ACTH reserve"; basal steroid excretion is normal, the menses are regular, and she is clinically euthyroid.

Case 2 demonstrates several difficulties that one may encounter in the surgical treatment of bilateral adrenal hyperplasia. The small adrenal remnant hypertrophied under constant ACTH stimulation, and approximately twenty months after the original operation, the symptoms of hyperadrenocorticism grad-

ually returned, requiring the removal of the residual adrenal tissue. At that time the presence of a pituitary adenoma was suggested by an enlarging sella and the pigmentation of the hands. Further growth of the pituitary tumor followed the complete removal of adrenal tissue, and the clinical picture of an ACTH-secreting adenoma developed.²⁶

This patient was treated in the same manner as Case 1 except that the pituitary gland received only 5000 rad of alpha particles in eleven days. This treatment was selected because there was not an urgent clinical need to suppress hormone production, and the dose was similar to that employed by us in the successful treatment of other pituitary tumors.¹⁶ The improvement has been less dramatic, but she began to show definite loss of skin pigmentation one year after treatment, and there was no further enlargement of the pituitary fossa. The thyroid and gonadal functions are normal. The plasma ACTH remains elevated, but it is still within the range observed in patients subjected to total adrenalectomy for adrenal hyperplasia.⁴⁰ Although this may represent some radiation resistance by this particular tumor further improvement may be anticipated because our previous studies have shown that the rate of pituitary suppression is determined by the dose of radiation — that is, a more rapid response might have been anticipated if the dose employed had been similar to that in Case 1. If further pituitary irradiation becomes necessary this may be given, for we have determined that much larger doses can be safely delivered to the pituitary fossa.

The successful treatment of these 2 patients with Cushing's disease has several important therapeutic implications. First of all, it has been shown that by the use of heavy particles, such as alpha particles and protons, one can teletherapeutically deliver larger amounts of ionizing radiation than can be administered by x-ray or gamma-ray sources. Secondly, this radiation can be accurately localized to the pituitary gland and delivered with little scatter, thus reducing the danger to surrounding central-nervous-system structures. Thirdly, a favorable skin-depth dose relation and greater biologic effectiveness can be achieved with these particles than from x-rays or gamma rays owing to a unique property of these penetrating particles referred to as the Bragg peak effect, which provides a Linear Energy Transfer (LET) like that in our original studies with neutrons.^{1,2} Although the Bragg peak was not employed in the treatment of the cases reported, it has been used in pituitary irradiation and other conditions¹⁴ and provides a means by which the dosage delivered to a desired depth not only is several times greater than the surface dose but also the effect per unit of dose is greater. Finally, it is suggested that these ideal teletherapeutic properties be used further in the treatment of Cushing's disease due to bilateral adrenal hyperplasia. Since cyclotrons

and other accelerators capable of delivering heavy particles are available in many medical centers throughout the world⁴¹ the preliminary studies reported here and in our previous papers can be applied widely in investigational and therapeutic studies.

SUMMARY AND CONCLUSIONS

Recent studies of pituitary and adrenal function as well as a greater awareness of pituitary tumors in patients with bilateral adrenal hyperplasia require that the pituitary gland again be considered primarily in the treatment of Cushing's disease. Two patients, 1 without a demonstrable pituitary tumor and another with an ACTH-secreting pituitary adenoma, were successfully treated by pituitary irradiation with alpha particles, which were imparted extremely high energies in a large accelerator. A third patient, previously untreated, received heavy particles to the pituitary gland in May, 1963, and now has signs of metabolic improvement. These penetrating heavy particles provide a more satisfactory form of teletherapy than x-ray or gamma-ray sources because larger amounts of ionizing radiation with a greater biologic effect can be delivered safely to the sella turcica, with little scatter and a favorable skin-depth dose relation.

We are indebted to Dr. Peter Forsham, director of the Metabolic Unit, University of California Medical Center, and Dr. Laurance Kinsell, director of the Institute for Metabolic Research, Highland Alameda County Hospital, who referred their patients to us and gave us valuable advice and co-operation in the subsequent study and care of these patients, and also to Dr. Don Nelson, of the University of Southern California School of Medicine, for performing the plasma ACTH assays.

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