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Cushing's syndrome treated by intrasellar implants of radioactive yttrium

Report of Five Cases

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Cushing's syndrome is due to an excess of circulating cortisol usually from the zona fasciculata and the zona reticularis of the hyperplastic adrenal cortex. In approximately 20 percent of the patients this excessive cortisol production arises from an adrenocortical adenoma. The disorder may also be associated with a chromophobe adenoma of the anterior pituitary which produces an excess of adrenocorticotropic hormone (ACTH), or as a result of hyperproduction of ACTH-like substance from a variety of tumors not of the pituitary, notably thymic tumors and bronchogenic carcinomata.

Cushing[1] believed that the pituitary was responsible for the syndrome, but for many years this concept was doubted, and an inherent abnormality in the adrenal cortex was thought to be the cause.[2, 3] The probable pathogenetic mechanism in most instances of Cushing's syndrome is adrenocortical hyperplasia due to an excess of ACTH.

Evidence to support this statement is as follows. Several cases of pituitary tumors occurring after adrenalectomy for Cushing's syndrome have been reported.[4] Although such tumors appear after adrenalectomy for Cushing's syndrome due to adrenal hyperplasia, they have not been seen after adrenalectomy in patients with metastatic cancer nor in those with spontaneous Addison's disease.[5] This, then, seems to imply strongly that the pituitary is being affected abnormally in Cushing's syndrome, and raises the possibility of neural stimulation of the pituitary. In some such cases the titer of ACTH in the blood is much higher than that found in patients with Addison's disease.[6] It would seem likely that this propensity to excessive ACTH production antedated adrenalectomy and was exaggerated by it. Suppression of corticosteroid production by administration of steroids occurs less readily, or less completely, in Cushing's syndrome associated with hyperplasia than in the normal subject. This fact may point to an increased force behind ACTH production in this condition.[7]

Nelson, Meakin, and Thorn[5] demonstrated the presence of excessive

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amounts of ACTH in 9 of 10 patients in whom, after they had undergone adrenal surgery for Cushing's syndrome, pituitary tumors developed. The concentration of ACTH in those patients was higher than that found in patients with Addison's disease. The authors were not able, however, to detect excessive ACTH in patients with untreated Cushing's syndrome.

The fact that the majority of patients with Cushing's syndrome are hyperreactive to ACTH has not been explained. It may be due to some other associated neural or pituitary factor, as Jailer, Longson, and Christy believe.[8]

For Cushing's syndrome due to cortical hyperplasia, partial or complete adrenalectomy has been the most commonly used therapy to the present time. Although adrenalectomy has generally been an efficient method, nevertheless, there are obvious disadvantages such as the distinct surgical risk involved. When the adrenalectomy is partial, the remaining fragment may not be sufficient to sustain life during stressful situations. When the adrenalectomy is complete, Addison's disease is substituted for Cushing's syndrome, and, unfortunately, in some patients pituitary tumors develop or the growth of existing ones increases. These tumors are a specialized type of chromophobe adenoma that often are large and may cause damage by local pressure. Furthermore, the tumors may be associated with deep pigmentation of the skin.

Since the basic etiology of Cushing's syndrome is not known, and no present therapy is available to influence the secretion of the hypothalamic ACTH-releasing factor, an attack on the pituitary itself seems the logical approach to treatment. Hypophysectomy in the treatment of Cushing's syndrome has been attempted in such a variety of ways as to suggest that the ideal method is yet to be found. Surgical removal has been used. X-ray irradiation, ^{60}cobalt teletherapy, and radon seed implantation have proved unsatisfactory.[9, 10] Likewise, the use of radioactive gold (^{198}Au) implantation has been tried and generally abandoned.[11, 12] Recently proton beam irradiation has been reported by Linfoot and associates[13] and by Lawrence and associates[14] as an effective means of pituitary destruction. Utilization of a cryosurgical probe[15] and also ultrasonic waves[16] as a means of obliterating the pituitary have been advocated. The use of radioactive yttrium (^{90}Y) for implantation in the hypophysis to create tissue necrosis has had wide use by Joplin,[12] Forrest, Blair, and Valentine,[17] and Molinatti and associates.[18] We have treated 300 patients with intrasellar implants of ^{90}Y for a number of conditions; namely, metastatic breast disease, metastatic prostatic cancer, diabetic retinopathy, acromegaly, and Cushing's syndrome.[19-22] This report reviews briefly our experience with the use of this method in the treatment of five patients with Cushing's syndrome.

Methods

We have used the technic of Forrest and Peebles Brown[10] for implanting ^{90}Y into the pituitary fossa. We are indebted to Professor Forrest for having

personally demonstrated the method in our early few cases. This method utilizes the fixation of ^{90}Y beads in place in the sella turcica by means of nylon capsules and stainless steel screws. The procedure is constantly monitored with an image intensifier and with the use of a simple guiding instrument. The technic has been described in an earlier report.[20] Each patient was evaluated preoperatively with a complete battery of endocrine assays that were then repeated at intervals after implantation. We are indebted to Dr. Grant W. Liddle of Vanderbilt University School of Medicine for measurement of the plasma-ACTH content in these patients. Considerable emphasis was placed on the use of the metyrapone test for measuring the degree of pituitary ablation.[6] In this test the administration of metyrapone prevents the production of cortisol in the adrenal cortex, resulting in the release of an excess of ACTH if the hypothalamic-pituitary complex is intact, which stimulates the adrenal gland to produce an excessive amount of urinary 17-ketosteroids and 17 hydroxycorticoids. In patients whose pituitary glands have been destroyed, production of ACTH is impossible, and thus there is no increase in the urinary steroid excretion.

Report of cases

Case 1. A 38-year-old Caucasian woman was first examined at the Cleveland Clinic in November 1963, five years after a diagnosis of Cushing's syndrome was made. The onset of symptoms of the disease was in 1956, with elevated blood pressure, moon facies, and amenorrhea. In 1958, she underwent bilateral partial adrenalectomy after which her skin became deeply pigmented. One year before examination by us diplopia developed, and roentgenograms of the skull showed an enlarged sella turcica. Her physical appearance was typical of Cushing's syndrome. Her weight was 146 pounds, height 64 in., and blood pressure was 116/86 mm Hg. Pigmentation was deep over the face and pressure areas, buccal mucosa, and was associated with black freckles. The visual fields were normal. There was a left lateral rectus palsy. Although the 17-ketosteroid and 17-hydroxycorticoid values were low, the circulating ACTH level was approximately one thousand times normal.

In November 1963, an attempt was made to implant two ^{90}Y beads into the pituitary, but a deviated nasal septum permitted only one pellet to be inserted; it delivered 4.8 mc of radioactivity. Postoperatively there was no complication; the diplopia regressed considerably but the sixth nerve paresis (palsy) was still demonstrable.

In June 1965, after tests showed consistently increased serum calcium content with normal urinary calcium excretion, a parathyroid adenoma was diagnosed and removed. Subsequently the serum calcium values returned to normal. In July 1965, a submucus resection of the nasal septum was performed, which allowed in the next months the removal of the first ^{90}Y pellet and the implantation of two other pellets with a combined radioactivity of 10.94 mc.

Eight months after the second ^{90}Y implant the patient was symptom-free but cortisone-dependent, requiring 12.5 mg b.i.d. Her skin color though still deep brown was somewhat lighter than preoperatively. She had good energy. Endocrine evaluation, including the metyrapone test and measurement of the serum growth hormone content, indicated a state of severe hypopituitarism. The plasma ACTH value, however, was still quite high.

The patient was last examined in May 1968, two years and nine months after the second ^{90}Y implant. She was symptom-free but still cortisone-dependent. Her skin color had faded little, if at all. Her weight was 170 pounds, and her blood pressure 132/70 mm Hg. There was a large, soft, painless mass in the right lower part of the abdomen which proved to be a multilocular cyst of the ovary; unfortunately it was not assayed for ACTH-like material. Again, endocrine tests demonstrated that pituitary function was notably deficient. She had evidence of hypothyroidism according to laboratory tests. Her glucose

tolerance curve had now returned to normal; previously it had been in the diabetic range. The visual fields were normal, and the sella turcica was now normal according to roentgenograms.

Case 2. A 38-year-old Caucasian woman was first examined at the Cleveland Clinic in January 1965. She had the facial appearance typical of Cushing's syndrome. She was said to have had arterial hypertension, but her blood pressure at the time of our examination at first was 120/90 mm Hg during a course of antihypertensive therapy. She had facial erythema and mild hypertrichosis (*Fig. 1A*). The skin was abnormally thin on the forearms; acne was present over the chest and back, and there were violaceous abdominal striae. Laboratory tests confirmed the clinical diagnosis of Cushing's syndrome. The plasma ACTH concentration was considered elevated (0.15 milliunit per 100 ml). She had a diabetic glucose tolerance curve. The visual fields were normal, and the sella turcica appeared to be normal on a roentgenogram.

On February 11, 1965, two ^{90}Y pellets were implanted in the pituitary fossa; the combined radioactivity was 10.24 mc. The postoperative period was without complication, and her appearance began to become normalized noticeably within a week. Mild diabetes insipidus developed, which soon regressed without treatment. Preoperatively she required 15 units of lente insulin and 5 units of semi-lente insulin daily, and one week postoperatively she required only 0.5 g of tolbutamide daily to control the hyperglycemia. Approximately two months postoperatively her appearance approached normal, and her blood pressure was 130/95 mm Hg.

Seven months postoperatively she showed evidence of complete hypophysectomy according to endocrine tests. She had had only one menstrual period postoperatively, and urinary gonadotropins were not measurable. The glucose tolerance test was still abnormal with a diabetic curve. Symptoms of myxedema appeared which required replacement therapy.

Two years postoperatively she felt active and energetic and would go swimming twice a week. Her appearance was normal (*Fig. 1B*). She continued with the course of replacement therapy, and in fact became quite weak with cessation of the administration of dexamethasone. This occurrence prevented completion of the metyrapone test, which fact together with other laboratory evidence indicated hypophysectomy had been total.

Three years postoperatively she had remained well, and demonstrated no clinical or laboratory evidence of Cushing's syndrome. Likewise she had remained in the typically hypophysectomized state.

Case 3. A 36-year-old Caucasian woman was first examined at the Cleveland Clinic in February 1963. She had a buffalo hump and the typical facial appearance of Cushing's

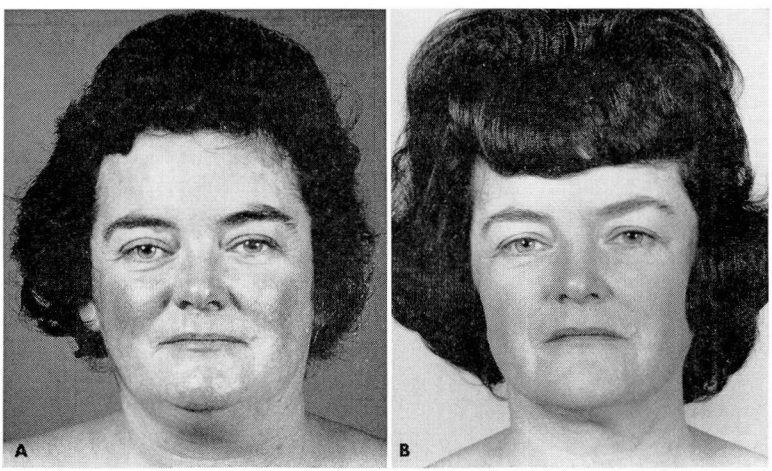

Fig. 1. Case 2. A, before ^{90}Y implantation; B, 24 months after ^{90}Y implantation.

syndrome (Fig. 2A). In the preceding seven months she had four episodes of sudden falling, during one of them she was briefly unconscious. She was plethoric, and she mentioned that she had weakness, and pain in the back. She was 63 in. tall, weighed 243 pounds, and had a moderately heavy beard. Her blood pressure was 160/120 mm Hg. She had a congenital strabismus.

The patient was diabetic and required 20 units of lente insulin and 20 units of semilente insulin in a single morning dose daily to achieve normal blood glucose levels. Roentgenograms of the sella turcica and visual fields were normal. There was mild spinal osteoporosis. An assay of the fasting serum ACTH showed an increased content of 0.57 milliunit.

On April 19, 1963, a transsphenoidal ^{90}Y pituitary implantation was performed. The radioactivity of the sources was calculated to be a total of 10.09 mc. Postoperatively transient diabetes insipidus developed. The patient was given a maintenance course of cortisone, at first 25 mg b.i.d., and later 12.5 mg b.i.d. At five months postoperatively she reported that the muscle aching and pain in the back disappeared. Symptoms of hypothyroidism were noted and were confirmed by laboratory tests; a regimen of desiccated thyroid was begun. She lost 13 pounds, and her blood pressure fell to 130/80 mm Hg. The glucose tolerance curve returned to normal while she was taking tolbutamide 0.5 g per day. Her facial appearance had improved notably but she was still obese. Eight months postoperatively while she was taking no hypoglycemic agent, the glucose tolerance test remained normal. Seventeen months postoperatively she had a normal appearance (*Fig. 2B*). She was last seen five years after ^{90}Y implantation, at which time she had remained free of any symptoms of Cushing's syndrome. She still was obese and weighed 222 pounds. Her blood pressure was in the range of 140/90 mm Hg. She still had to shave every day. Roentgenograms of the sella turcica were normal, as were visual fields. Endocrine assays still showed evidence of complete or nearly complete hypophysectomy with accompanying hypothyroidism.

Case 4. A 44-year-old Caucasian woman was first examined at the Cleveland Clinic on January 18, 1965, because of nausea, vomiting, headaches, and nervous irritability. She had not felt well for five years. During that time she had gained more than 20 pounds, chiefly over the trunk. She had generalized aching pain, and weakness of the arms and legs. Her blood pressure had been high, at times being more than 200 mm Hg for at least two years, and recently she was found to have diabetes mellitus. Her face had become somewhat hirsute, and menses had stopped six years previously.

Examination showed the facies suggestive of Cushing's syndrome, temporal balding, abnormally thin skin, and ecchymoses over the forearms. She was 62–¾ in. tall, weighed 149 pounds, and her blood pressure was 210/130 mm Hg. The genitalia were normal

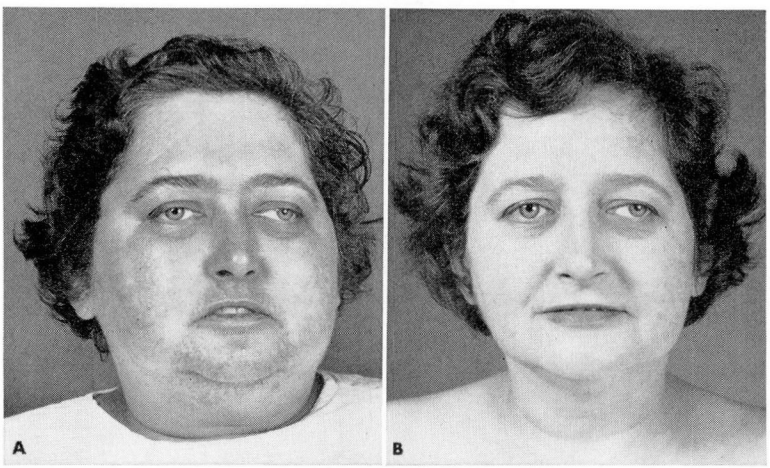

Fig. 2. Case 3. A, before ^{90}Y implantation; B, 17 months after ^{90}Y implantation.

except for an enlarged clitoris. Her visual fields were normal. The sella turcica showed no abnormality on a roentgenogram. An adrenal angiogram was normal. The blood ACTH content was 0.15 milliunit, considered elevated, but the actual figure probably was invalid due to prolonged storage of the specimen of blood. A glucose tolerance test denoted diabetes, and the blood cortisol levels were consistent with the diagnosis of Cushing's syndrome.

On February 11, 1965, two sources of ^{90}Y were implanted in the sella turcica; the combined radioactivity was 10.07 mc. The patient's postoperative course was stormy, and was complicated by several generalized convulsions, active pyelonephritis, abnormal serum sodium and potassium values, and diabetes difficult to control, not only because of the infection but because she was cortisone-dependent. She also had transient diabetes insipidus. Subsequently, improvement was steady but slow. Two months postoperatively endocrine tests demonstrated a hypophysectomized state with hypothyroidism, and improvement in the results of the glucose tolerance test. Twenty-six months postoperatively the patient had mild anorexia and mild diabetes insipidus but no other symptoms. She weighed 132 pounds and her blood pressure was 160/90 mm Hg. She looked normal and healthy. Her glucose tolerance test was normal. She showed evidence of hypothyroidism and hypopituitarism. In September 1968, two years and seven months postoperatively, she was well and happy and was working steadily as a bookbinder.

Case 5. A 39-year-old Caucasian woman was first examined at the Cleveland Clinic on April 10, 1963, having had a diagnosis of Cushing's syndrome and pituitary tumor made previously in 1949. At that time she had undergone pituitary irradiation, and good remission of the symptoms ensued. She then did well until 1960, when the manifestations of the disorder returned. She noted dryness of the skin and hyperpigmentation, blurred vision, increased appetite, tiredness, amenorrhea, headaches, and backaches. Arterial hypertension was observed one year before, in 1962. Examination demonstrated changes typical of Cushing's syndrome (*Fig. 3A*), including plethoric moon face with hypertrichosis, buffalo hump, hyperpigmentation of the skin, purpura of both arms, and generalized hypertrichosis. The blood pressure was 180/115 mm Hg. Visual field study demonstrated slight bitemporal loss for color. The sella turcica appeared to be normal on a roentgenogram.

Laboratory determinations disclosed erythrocytosis, a diabetic glucose tolerance curve, and increased urinary 17-ketosteroids and 17-hydroxycorticoids. Administration of dexamethasone phosphate in small and in large doses suppressed urinary excretion of 17-ketosteroids and 17-hydroxycorticoids.

On April 29, 1963, pneumoencephalography gave normal results, with no evidence of

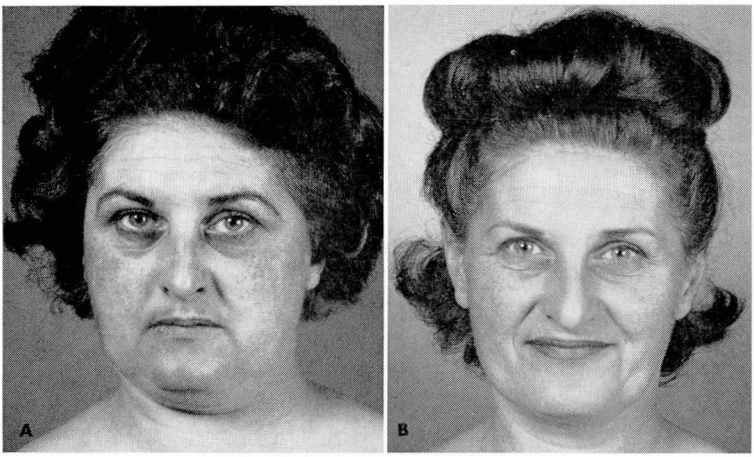

Fig. 3. Case 5. A, before ^{90}Y implantation; B, 36 months after ^{90}Y implantation.

a pituitary or a suprasellar tumor. On June 5, 1963, two ^{90}Y beads (9.6 mc) were implanted into the sella turcica. Three months postoperatively the patient had lost the physical manifestations of Cushing's syndrome. The skin appeared normal; blood pressure returned to normal; and the menses returned. She had lost 15 pounds. Endocrine assays including the metyrapone test indicated complete pituitary ablation.

Six months postoperatively the patient was continuing to do well and had no clinical evidence of Cushing's syndrome. Visual fields were normal. Endocrine assays suggested that there was some residual pituitary function. Evaluation one year postimplantation showed the patient again to have no evidence of Cushing's syndrome. She was unable to tolerate cessation of cortisone replacement therapy. Three years postoperatively she still showed a remission from Cushing's syndrome (*Fig. 3B*) and her endocrine tests still suggested the presence of some pituitary reserve.

In September 1968 she returned for a five-year postimplantation evaluation. At that time she demonstrated some early signs of recurrence of Cushing's syndrome as manifested by weight gain, return of skin hyperpigmentation, buffalo hump, hypertension, blurred vision, and mental depression for three months. Endocrine assays demonstrated no direct evidence of recurrence. Visual fields and roentgenograms of the skull were normal. She returned on May 24, 1969, for a six-year follow-up examination. She was having daily headaches and frequent visual blurring. She noted recent weight gain and increased facial roundness. The endocrine assays demonstrated definite response to the metyrapone test. She is to be restudied to exclude or to confirm the presence of a recurrent pituitary tumor.

Comment

Each of the five patients had a favorable change in both the clinical and laboratory manifestations of Cushing's syndrome after ^{90}Y hypophysectomy. The improvement was maintained in four patients (cases 1 through 4) for from three to five years. In the fifth patient (case 5) remission of the Cushing's syndrome was effected for over four years, but in the fifth year recurrence manifested itself.

In the four patients in whom remission has been maintained, urinary excretion of 17-ketosteroids and 17-hydroxycorticoids dropped to a low level postimplantation and has remained so. Likewise, the diabetic glucose tolerance curve and/or clinical diabetes was reversed in each of these four patients. They have each remained in an hypophysectomized state with clinical and laboratory evidence of secondary hypogonadism and hypothyroidism. Unfortunately, postimplantation circulating plasma ACTH levels have not been determined consistently enough for us to draw conclusions.

The fifth patient has had an apparent recurrence of Cushing's syndrome as well as pituitary tumor. Interestingly she has had reversal of the improvement in the endocrine assay findings as well. For example, the urinary excretion of 17-ketosteroids and 17-hydroxycorticoids is again increased. The metyrapone test demonstrates pituitary function, and the diabetes has recurred. Neither hypogonadism nor hypothyroidism has developed. Despite clinical and laboratory evidence of hypopituitarism in one patient (case 1), the hyperpigmentation of the skin cleared little if any. The pituitary tumor remained under control, however, as did the manifestations of Cushing's syndrome.

There were no complications of the ^{90}Y implantation in any of the patients except for mild diabetes insipidus in one patient (case 4).

Summary

Five patients with Cushing's syndrome were each treated by implanting ^{90}Y pellets into the pituitary. The disease was brought under control in each and remained so in four of the patients. In the other patient, recurrence took place after five years. No complication occurred as a result of the ^{90}Y implantation.

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