Stereotactic treatment of acromegaly¹

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The normal anterior pituitary is resistant to radiation. Tissue effects vary with the characteristics of the radiation source, time over which the radiation is delivered, and the interval between treatment and histological study. Nevertheless, over 20,000 r are required for significant necrosis (Kelly, Feldsted, Brown, Ortega, Bierman, Lowbeer, and Shimkin, 1951; Nickson, 1957; Plunkett, 1957; Lawrence, Tobias, and Born, 1958) and between 70,000 r and 190,000 r for complete destruction of either the human or primate gland (Rasmussen, Harper, and Kennedy, 1953; Greening, 1957; Notter, 1959).

The optic chiasm, hypothalamus, and other neuronal structures adjacent to the pituitary are relatively more sensitive (Rasmussen *et al.*, 1953). Although the report of Crompton and Layton (1961) of a case of fatal necrosis of these structures following 4,500 r over four weeks must be unusual, histological changes are characteristically found in the neuronal structures of the parasellar region after 6,400 r to 15,000 r of external gamma radiation to this area (Kelly *et al.*, 1951; Nickson, 1957; Crompton and Layton, 1961).

Growth hormone producing adenomas of the pituitary are more radiosensitive than the normal gland. They also appear to be often more radiosensitive than the surrounding neuronal structures. The margin of safety is, however, slight.

Although metabolic and endocrine studies of acromegalic patients following conventional doses of radiation by conventional sources have been disappointing (Beck, Schalch, Parker, Kipnis, and Daughaday, 1965; Greenwood, Stewart, Forrest, and Wood, 1965; Kozak, Vagnucci, Lauer, and Thorn, 1966; Drucker, Segal, Verde, and Christy, 1967; Roth, Glick, Cuatrecasas, and Hollander, 1967), Linfoot and Greenwood (1965) have treated acromegalic patients with up to 9,000 r of radiation to the sella with the proton beam and have reported delayed but significant decreases in plasma growth

hormone level. This paper describes our experience with interstitial implantation of single or multiple point sources of yttrium⁹⁰ in the treatment of acromegaly. Using an optimal dose of interstitial radiation, we anticipated that there would be a differential effect on the growth hormone producing adenoma of acromegaly with sparing of the normal pituitary remnant. In view of the above data, we decided that no portion of the adenoma should receive less than 9,000 r; no portion of the pituitary remnant, more than 20,000 r; and no significant volume of nervous tissue, more than 6,000 r.

In addition, several cases underwent cryogenic destruction of their gland, for reasons to be described below.

MATERIAL

As listed in Table I, 11 patients with acromegaly with documented intrasellar tumours without suprasellar extension have been treated with stereotactic surgery. Each of these was found to have elevated serum growth hormone levels, not suppressible to zero by an oral glucose load, thus confirming the diagnosis of acromegaly (Earll, Sparks, and Forsham, 1967). Eight of these cases received implantation of interstitial sources of yttrium⁹⁰ and three cases underwent central cryogenic destruction of their tumour. Of the eight cases treated with yttrium⁹⁰ four were males and four females. Their ages ranged from 18 to 56. Of the three patients treated with cryosurgery, two were males, and one was a female. Six of the 11 patients had had one or more courses of previous radiation two and a half to seven and a half years previously.

For reasons to be described below, those patients with severe erosion of the floor of the sella were selected for cryogenic surgery. Review of Table I indicates, as might be expected, that those cases with erosion of the floor of the sella were among the larger tumours in the series. There were, however, equally large tumours in the yttrium⁹⁰ treated group.

METHOD

In order to estimate the number, distribution, and strength of the yttrium⁹⁰ sources to satisfy the criteria

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TABLE 1
SUMMARY OF CASES

Patient	Previous x-ray therapy			Modality ¹	Dose	Pituitary function ²	Pre-op. ³	Post-op. (mth.)				
	Tumour dose (r)	Yr. previous	Size of tumour (mm)					2	8	12	18	24
1 E.L.G. 56 ♀			16 × 17 × 20	Y ⁹⁰ 2 r 0.8 mc	9,000 r	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	115 N N N N	50 N N N N	18 N N N N	25 N N N N	20 N N N N	23 N N N N
2 J.S. 42 ♀	6,300	7	14 × 11 × 18	Y ¹⁰ 1 r 1.3 mc	8,000 60,000 r	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	32 N N N L	23 N N N 0	6 N N N 0			
3 G.S. 51 ♀			10 × 10 × 16	Y ⁹⁰ 1 r 0.45 mc	10,000 r	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	36 N N N N	3 N N N N	5 N N N N		3 N N N N	
4 G.C. 53 ♂	3,500 2,500 1,500 4,000	20 17 14 4	19 × 23 × 22	Y ⁹⁰ 4 r 1.28 mc	10,000 r	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	111 N L L N	41 N L N L	5 N N N N			
5 M.L. 39 ♂	3,500	2½	17 × 12 × 16	Y ⁹⁰ 2 r 0.42 mc	10,000 r	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	23 N N L N	9 N N N N	3 N N N N			
6 H.S. 46 ♀	4,000	13	15 × 10 × 20	Y ⁹⁰ 1 r 1.3 mc	12,000 r	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	17 N L N L	5 N L N L	5 N N N N	6 N N N N		
7 R.G. 30 ♂	4,475	2½	23 × 21 × 16	Y ⁹⁰ 4 r 0.84 mc	12,000 r	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	25 L N L N	10 N N N N	16 N N N N			
8 A.K. 18 ♂			21 × 13 × 17	Y ⁹⁰ 4 r 1.96 mc	15,000 r	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	145 0 N L N	3 L L L N	2 N N L N	2 N N L N	2 N N N N	2 N N N N
9 S.A. 59 ♀	6,000	5	20 × 19 × 21	Cold	-180°C 6 min × 1	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	130 N L L	41 N L L	40 N N N	42 N N N		31 N N
10 J.B. 51 ♂			22 × 18 × 21	Cold	-180°C 15 min × 1	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	34 N N N N	2 N L 0	2 N L L	1 N L L		2 N L L
11 E.L. 54 ♂			18 × 19 × 23	Cold	-180°C 5 min × 2	Gr. horm. (mμg/ml.) Gon. Thyr. Adr. cor. Post. pit.	60 N N L L	6 N N N N	6 N N N N			

¹The mc are the sum of all rods used—each rod being of equal strength.

²Gr. horm. = growth hormone. Gon. = gonadotropin. Thyr. = thyroid. Adr. cor. = adrenal cortex. Post. pit. = posterior pituitary.

³N = normal, L = low, 0 = no detectable function.

of having no portion of the adenoma receive less than 9,000 r and no portion of the normal pituitary remnant more than 20,000 r, the assumption was made that the pituitary remnant would always be subcapsular in location. Personal experience, at craniotomy, would indicate that the pituitary remnant is usually situated posteriorly and superiorly, and this has been the experience of others (Ray, 1968).

Figure 1 is a semilog. plot of the radiation dose broadside to a 2×3 mm yttrium⁹⁰ rod of 0.21 mc and a similar rod of 1.3 mc—the lowest and highest activities used in this study. Dose is plotted against distance in millimetres. These values were calculated by the method of the Jones Survey (Jones, Mallard, and Elmanharawy, 1963) and the most recent available figures of Elmanharawy (1965) using the figure of 342,000 r/mc (total decay) at 1 mm broadside to the rod. The fall off in radiation dosage is steep, and approximately 3 mm from the surface of the 0.21 mc source and 5.2 mm from the surface of the 1.3 mc source, the radiation dose is approximately 12,000 r. This dose would seem ideal. Again referring to Fig. 1, 2 mm beyond the structure receiving this ideal radiation dose, tissue would receive

FIG. 1. A semilog. plot of the radiation broadside to a 2×3 mm yttrium⁹⁰ rod 0.21 mc, a similar rod 1.3 mc as labelled, calculated by the method of the Jones Survey and the most recent figures of Elmanharawy.

less than 4,000 r, a level well tolerated by the surrounding structures. Furthermore, the decrement continues to be rapid, and the total volume of neural tissue receiving radiation is small.

Figure 2 includes AP and lateral radiographs of a sella $21 \times 13 \times 17$ mm, containing four yttrium⁹⁰ rods 0.49 mc each. Above the radiographs is a diagram of the isodose curve in one plane around these rods. The radiation dose in the cross-fire between the rods is exceedingly high. If the rods are placed more than 5 mm apart, however, the effect of one rod system on the region lateral to its neighbour is negligible.

Thus, by appropriate positioning of single or multiple sources of yttrium⁹⁰ in the sella turcica, a relatively uniform and critical level of radiation source can be administered to the border of the tumour mass without excessive radiation to the pituitary remnant. Furthermore, little radiation will be received by a significant volume of neuronal tissue.

In order to space the radiation sources to give reasonably uniform dose of radiation to the periphery of the tumour, a reliable estimate of the size and shape of the tumour was needed.

PLAIN RADIOGRAPHS Radiographs and laminograms of the sella turcica were obtained and the width, height, and length of the sella were determined as described by DiChiro and Nelson (1962) and corrected for magnification.

PNEUMOENCEPHALOGRAPHY In several cases, a complete pneumoencephalogram was performed several days before surgery. In general, just before stereotactic surgery, the patient was placed in a sitting position and air was introduced into the suprasellar region via a lumbar spinal needle. The suprasellar air shadow was used to make appropriate corrections in rod placement if the superior border of the tumour was not in the anticipated position.

ARTERIOGRAPHY Before or during surgery, each patient underwent bilateral carotid arteriography. Lateral displacement of the carotid siphon was taken into account in estimating the lateral margins of the tumour.

RETROGRADE CAVERNOUS ANGIOGRAPHY In each case, the patient underwent retrograde cavernous angiography as described by Hanafee, Rosen, Weidner, and Wilson (1965), thus demonstrating another structure presumably immediately lateral to the sella contents.

As a first approximation, the width of the floor of the sella was considered as the width of the tumour. In no case was it necessary to revise this estimate by more than 4 mm. In nine cases in which the lateral view of the carotid siphon crossed squarely over the central portion of the sella turcica (Fig. 3), the medial border of the carotid artery and the medial border of the cavernous sinus were the same distance from the midline. In two cases, the carotid siphon was opened and displaced anteriorly, presumably by tumour mass. In these instances, the cavernous sinus was lateral to the medial border of the carotid artery, as seen on x-ray examination.

FIG. 2. (Below) Lateral and AP radiographs of the final placement of the interstitial radiation in A.K., received 15,000 r at the gland margin. There is a single Forrest screw each side of the midline. Each screw is tipped with two 0.49 mc yttrium⁹⁰ rods spaced by a 2 mm plastic blank. (Above) A diagram of the isodose curve in one plane around these rods. The radiation dose in the cross fire between the rods is exceedingly high. If the rods are placed more than 5 mm apart, however, as they are in this case, the effect of one rod on the region lateral to its neighbour is negligible.

FIG. 3. Lateral and AP views of a carotid angiograph of R.G. Note that the carotid siphon passes squarely over the centre of the enlarged sella turcica in the lateral view. In such cases cavernous sinus angiography shows the medial border of the cavernous sinus and the medial border of the carotid siphon to be the same distance from the midline and both presumably reflect the lateral extension of the tumour.

In all cases, yttrium⁹⁰ sources or the cryogenic probe were introduced via the transnasal route using the Rand-Wells stereotactic apparatus, as previously described (Rand, Dashe, Paglia, Conway, and Solomon, 1964).

Previous experience (unpublished data) has shown that yttrium⁹⁰ sources placed freely in tissue will migrate in the direction of gravity. The use of free yttrium⁹⁰ sources, therefore, would mitigate against careful calculation of tumour size and accurate placement of the sources. The yttrium⁹⁰ rods were accordingly fixed by a modification of the screw described by Forrest, Blair, Peebles Brown, Stewart, Sandison, Harrington, Valentine, and Carter (1959).¹ This is a stainless screw, tipped with a nylon sheath of varying lengths. Yttrium⁹⁰ rods can be placed within the sheath and plastic blanks placed between the rods for positive fixation and spacing of the radiation sources. At the top of Fig. 4 is photographed a Forrest screw tipped with an 8 mm nylon sheath containing two 3 mm yttrium rods spaced by a 2 mm plastic blank. Beneath this is a second Forrest screw tipped with a 3 mm sheath containing a single yttrium rod. Below these are the disassembled components. In the cases under discussion, a single midline screw was used or two screws, one each side of the midline, containing one or more rods. As listed in Table I, one to four rods were used with a total dose of 0.8 to 2 mc.

In order to place these screws in the sella, guides and screwdrivers designed by Forrest were used.¹ These are readily adaptable to the Rand-Wells stereotactic guide, by placing a suitable bushing in the probe carrier.

The patients were placed in the stereotactic headrest and, under x-ray control, the screws were fixed in the floor of the sella turcica, with the nylon sheaths extending through the tumour mass. This method of fixation proved adequate in cases in which the sella floor was not severely eroded. In cases in which the floor of the sella turcica was demineralized and thinned, the tumours were treated stereotactically, using a cryoprobe, 4.76 mm in diameter.² The number of lesions and time of freezing are summarized in Table I. In each case, the freezing temperature was -180°C . One or two centrally placed cryogenic lesions were used. The success of such lesions has been previously published, along with the development and rationale for this technique (Rand *et al.*, 1964). Lateral to the sella contents is the rapidly flowing blood contained in the cavernous sinus and carotid arteries. Superiorly, spinal fluid is circulating in the suprachiasmatic and prepontine cisterns. These body fluids, being at body temperature, are warm, relative to the tissue being frozen. Thus, these structures act as a heat sink and might well protect the subcapsular tissue adjacent to these structures from cold damage. A centrally placed lesion might well not affect the more peripheral portion of the sella contents, at least laterally, superiorly, and posteriorly; and thus preserve the pituitary remnant.

In order to protect the surrounding neuronal structures from excessive cold, the cryogenic surgical procedures

¹Obtained from the London Splint Company, Ltd., 50-52 New Cavendish Street, London W.1, England.

²Linde CE-2A Cryosurgery Unit.

FIG. 4. Shown from above down are: a Forrest screw tipped by a nylon sheath 1 cm long and containing two 3 mm yttrium rods spaced by a 2 mm plastic blank, a Forrest screw tipped with a 4 mm sheath containing a 3 mm yttrium rod, a 1 cm nylon sheath, a 3 mm $\times$ 2 mm yttrium rod, a 2 mm $\times$ 2 mm plastic blank, and a 2 mm $\times$ 2 mm yttrium rod.

were performed under local anaesthesia with the patient awake. Visual fields, visual acuity, and extraocular movements were tested continuously during the active freezing of the probe tip, as previously described (Rand *et al.*, 1964). Yttrium⁹⁰ implantations were performed under general anaesthesia. Before introduction of the destructive medium, a biopsy needle was stereotactically introduced into the sella turcica, and a biopsy confirming an eosinophilic adenoma was obtained in each case. Each patient was admitted to the hospital for extensive metabolic and endocrine evaluation before the above procedures, and subsequently, two months post-operatively and then at intervals, usually of six months.

To date, the patients have been followed for from eight months to 24 months since operation. Studies have included:

GONADOTROPINS Two 24-hour urine samples were analysed for gonadotropins by the method of Bradbury, Brown, and Brown (1949)¹ Two 24-hour urine samples were collected for 17-ketosteroids (Drekter, Heisler, Scism, Stern, Pearson, and McGavack, 1952). In females, a vaginal smear was evaluated for oestrogen effect (Young, Bulbrook, and Greenwood, 1957).

THYROID FUNCTION Studies included I¹³¹ uptake for three, five, and 24-hour reading, protein bound iodine,¹ T4 by column,¹ and serum cholesterol.¹

ADRENOCORTICAL FUNCTION Urine 17-hydroxycorticosteroids were determined after methopropione stimulation as described by Liddle, Estep, Kendall, Carter, Williams, and Townes (1959). Plasma 17-hydroxycorticosteroids were measured by the method of Nelson and Samuels (1952) and the diurnal variation was determined on two separate occasions as was the plasma 17-hydroxycorticosteroids response to 25 u. intravenous ACTH described by Christy, Wallace, and Jailer (1955). Plasma 17-hydroxycorticosteroids were determined before and after stress stimulation with insulin induced hypoglycaemia (Landon, Wynn, and James, 1963).

INTEGRITY OF VASOPRESSIN SECRETION This was evaluated by determining blood and urine osmolarities after 12 hours of water deprivation (Dashe, Cramm, Crist, Habener, and Solomon, 1963).

SERUM GROWTH HORMONE This was measured by radioimmunoassay (Schalch and Parker, 1964). Fasting samples were obtained on hospitalized patients early in the morning. A Courmand needle was placed in the antibrachial vein, and subsequently the patient was kept at complete bedrest for at least 30 minutes before two samples were drawn, 15 minutes apart. These duplicate samples were obtained on three separate occasions, during each admission. Each sample was analysed in duplicate.

RESULTS

Figure 5 charts the mean fasting resting growth hormone level of each patient, pre-operatively, and periodically post-operatively, for up to 24 months. The total variation is indicated. The eight cases treated with interstitial yttrium⁹⁰ are arranged in order of increasing dose of radiation at the gland margin, with the exception of the second case. In this case, a single central rod of 1.3 mc was implanted 2 mm higher than desired. Thus, the calculated dose at the superior border of the gland was 60,000 r whereas the inferior border received but 8,000 r. All cryogenic lesions were made at -180°C. The

minutes of freezing for each lesion and the number of lesions are indicated.

To the right, the bar labelled 'normal' indicates the average and variation of resting fasting growth hormone as determined in our laboratory on 157 non-acromegalic subjects. These subjects had carcinoma of the breast, carcinoma of the prostate, and lumbar disc disease. Patients with intracranial disease, overt diabetes mellitus, or other known endocrine disorders were excluded. These values are consistent with normal values reported by others (Unger, Eisentraut, Madison, and Siperstein, 1965).

Table I summarizes these same 11 cases, including details of previous conventional radiation, the size of their tumours, and the therapeutic modality employed. The right side of Table I summarizes the pre-operative and post-operative endocrine studies on these patients. The average plasma growth hormone levels in mμg/ml., as charted in Fig. 5, are listed horizontally. Beneath the growth hormone levels, the gonadotropin, thyroid, adrenal cortex, and posterior pituitary functions are summarized. The results of the tests, described under Method, are synthesized as being N (normal), L (low), and 0 (no detectable function).

Table II summarizes this data for the yttrium⁹⁰ treated cases pre-operatively and at the time of their last follow-up evaluation, eight to 24 months after surgery. Results are grouped as 'normal' or 'abnormal'. Abnormal in respect to growth hormone indicates excessively high plasma levels, whereas abnormal in respect to other pituitary functions indicates subnormal baseline levels or subnormal response to the provocative tests listed above.

Of the eight cases undergoing yttrium⁹⁰ implantation and receiving 9,000 r to 15,000 r to the entire gland margin, all eight had excessively high growth hormone levels pre-operatively and two of these (Case 1 and Case 7) continue to have elevated, although diminished, fasting growth hormone levels. Case 1 received the lowest dose of radiation in the

TABLE II
TREATED CASES OF ACROMEGALY. YTTRIUM⁹⁰ IMPLANTS
(EIGHT CASES)

Pituitary function	Pre-operative abnormal ¹ cases (no.)	Last follow-up (8-24 months) abnormal ¹ cases (no.)
Growth hormone	8	2
Gonadotropin	2	0
Thyroid	2	0
Adrenal cortex	4	0
Posterior pituitary	2	1 ²

¹'Abnormal' indicates excessively high growth hormone level or insufficiency of the other pituitary functions listed.

²On replacement therapy.

¹Bio-Science Laboratories, Van Nuys, California, U.S.A.

FIG. 5. The pre-operative and serial post-operative growth hormone levels of each patient. The average of each set of determinations and the total variation of these determinations is depicted. The cases treated with yttrium⁹⁰ interstitial radiation are arranged in the top row in order of ascending dose of radiation at the gland margin, with the exception of Case 2, whose eccentric placement led to a variable dose at the gland margin. Below are the growth hormone levels of the three cases treated with stereotactic cryosurgery. The time in minutes is listed followed by the number of lesions. All lesions were made with the 4.76 mm cryoprobe supplied with the Linde CE-2A apparatus. The time in each case is the time at which the probe was being actively cooled at minus 180°C.

series, 9,000 r to the gland margin. She had a significant drop in growth hormone level from 115 mμg/ml. to approximately 20 mμg/ml., over the first eight months, but subsequently has been followed for a total of 24 months post-operatively without further decrease in her growth hormone level. Case 7 received 12,000 r to the tumour margin, a level which has been highly successful in other patients, but, eight months post-operatively, has failed to show complete ablation of excess growth hormone.

Pre-operatively, several of the yttrium⁹⁰ treated group had deficiencies in one or more other pituitary functions. As seen in Table I, there was a progressive improvement in other pituitary functions over a matter of months, up to 18 months. At this time, eight to 24 months post-operatively, all patients

have had a return of other pituitary functions to normal with the exception of Case 2 (J.S.) who, presumably due to excessively high placement of the yttrium⁹⁰ rod, has developed overt diabetes insipidus. Pre-operatively she was unable to concentrate her urine after an overnight fast. Post-operatively she required Pitressin which she continues to take, although the severity of her diabetes insipidus continues to lessen.

Three cases underwent cryogenic therapy. As seen in Table I, all three tumours were of approximately the same volume. Cases 9 and 10 were spherical and Case 11 oval with the greatest diameter corresponding to the width of the sella turcica. For this reason, Case 11 received two cryogenic lesions, centred 4 mm each side of the midline, whereas Cases 9 and 10 were treated with single midlines.

lesions of six to 15 minutes, respectively. Of the three cases, only one continues to have an elevated growth hormone level, although this dropped from 130 to levels of between 31 and 42 m μ g/ml. This result followed a single midline lesion at -180° for six minutes. By contrast, Case 10 received a single midline lesion for 15 minutes and had complete ablation of growth hormone but developed severe anterior and posterior pituitary insufficiency, which, although it has improved over 24 months, continues. He initially required cortisone and Pitressin replacement and continues to require the former. The patient tolerated mild hypothyroidism for one year without improvement and subsequently was given oral replacement. By contrast, Case 11 had satisfactory ablation of growth hormone with preservation of other pituitary functions. In fact, pre-operatively, there were deficiencies in adrenal cortex and posterior pituitary functions which reverted to normal within two months of treatment.

Table III summarizes the endocrine status of the three cases treated with cryosurgery, pre-operatively and at the time of their last follow-up eight to 24 months after treatment. As previously stated, one of the three growth hormone levels remained above normal. Pre-operatively, two cases had deficiencies in adrenal cortex and posterior pituitary function. The last post-operative evaluation revealed one instance of thyroid deficiency and one instance of adrenal cortex deficiency, both requiring replacement therapy. Analysis of the details in Table I reveals that the minor abnormalities pre-operatively had reverted to normal and that the two severe abnormalities, requiring replacement therapy, occurred in Case 10, who had normal pituitary function pre-operatively. These results indicate that it is possible to ablate growth hormone producing adenomas with cryosurgery. Furthermore, it is possible to do this with preservation of the pituitary remnant and, on occasion, improvement in function of the remaining pituitary. In contrast to the

radiation treated group, however, it is difficult to predict parameters that will lead to this optimal therapeutic result. A review of tumour sizes and the parameters of destruction indicate that minor differences in technique produce major differences in results.

CLINICAL CHANGES Pre-operative symptoms included weakness, increased sweating, headaches, and arthralgia in all cases. With the exception of Cases 4 and 7, both last evaluated eight months after treatment, all cases had complete relief of symptoms. Case 4 continues to have arthralgia, which is attributed to his far-advanced acromegaly, and severe joint deformities. Case 7 continues to have headache and arthralgia, which is attributed to incomplete growth hormone ablation. Nevertheless, all other cases, even with incomplete ablation, have had a gratifying clinical response. In most cases with a progressive drop in growth hormone level, symptomatic relief has characteristically preceded the maximum therapeutic effect, as measured by fall in growth hormone.

Reversal of acromegalic features is variable. Soft tissue changes around the eyes and nose and marked soft tissue absorption in the hands and feet with a concomitant decrease in glove and shoe size occurred in all cases. Younger patients and those with a shorter history of clinically evident disease responded more favourably. Serial radiographs of the face, hands, and feet have failed to show decrease in the distinctive changes of acromegaly or in the size of the bones to date. Decrease in the size of the sella turcica, however, has been the rule in most cases observed for over one year. In one case, Case 10, pneumoencephalography was performed 18 months after surgery and outlined a considerable decrease in the volume of the intrasellar contents.

Table IV summarizes the diabetic status of the cases pre-operatively, and at the time of their last evaluation, eight to 24 months after surgery. The blood sugar was elevated in nine of the 11 cases pre-operatively. Six of these returned to normal. The glucose tolerance test (100 g glucose orally) was abnormal in 11 cases pre-operatively and four of these have returned to normal. Two of the patients

TABLE III

TREATED CASES OF ACROMEGALY. CRYOSURGERY (THREE CASES)

Pituitary function	Pre-operative abnormal ¹ cases (no.)	Last follow-up (8-24 months) abnormal ¹ cases (no.)
Growth hormone	3	1
Gonadotropin	0	0
Thyroid	0	1 ²
Adrenal cortex	2	1 ²
Posterior pituitary	2	0

¹'Abnormal' indicates excessively high growth hormone level or insufficiency of the other pituitary functions listed.

²On replacement therapy.

TABLE IV

THE 'DIABETIC STATUS' OF THE PATIENTS UNDER STUDY (11 CASES)

Clinical status	Pre-operative	Post-operative
Elevated F.B.S.	9	3
Abnormal G.T.T.	11	7
On treatment for diabetes	2	0

required therapy for diabetes mellitus pre-operatively. G.S. took an oral hypoglycaemic agent and E.L. took 60 u. NPH insulin daily. Both had successful ablation of excess growth hormone. Post-operatively neither required their therapy for diabetes; G.S. now has a normal fasting blood sugar and a slightly abnormal glucose tolerance curve; E.L. has a borderline to elevated fasting blood sugar and a moderately elevated glucose tolerance curve. One patient (J.B.) had a bilateral carpal tunnel syndrome pre-operatively and another (G.C.) had a severe peripheral neuritis. The former did not improve for 18 months but responded to local surgery at the wrist. The latter has not improved during eight months of follow-up examination.

COMPLICATIONS Table V lists the potential complications and their incidence, transient and permanent, in the cases under discussion. There was no incidence of rhinorrhoea, bacterial meningitis, or optic nerve damage. There were two cases of transient cranial nerve palsy, a sixth nerve in one yttrium⁹⁰ implant and a third nerve in one cryogenic operation. Both of these were delayed for several days and lasted a matter of weeks. The delayed onset and transient character of the deficits suggests that they were secondary to swelling of the tumour, post-operatively. One cryogenic case developed permanent anterior pituitary insufficiency. Evaluation of posterior pituitary function two months after surgery revealed, in two cases, inadequacy of urinary concentration after 12 hours of water deprivation. A third case had clinically evident diabetes insipidus. The former two cases proved to be transient, and a third case continues to require Pitressin snuff, eight months after surgery.

TABLE V
INCIDENCE OF COMPLICATIONS

	Transient	Permanent
Rhinorrhoea	0	0
Bacterial meningitis	0	0
Optic nerve damage	0	0
Paresis III, IV, or VI	2	0
Pituitary insufficiency		
anterior	0	1
posterior	2	1
Epistaxis	1	
Appendicitis	1	

Transnasal operative manipulation was accompanied in all cases by minor degrees of nasal haemorrhage. In one case this was significant. Case 1 (E.L.G.) returned two weeks after the yttrium⁹⁰ implantation with brisk nasal bleeding.

Radiographs of the skull revealed a change in position of one of the yttrium⁹⁰ screws. She received a unit of blood while in the emergency room. In retrospect, this was probably not necessary.

One patient developed appendicitis and peritonitis one week post-operatively. He was not on steroid therapy at this time and the associated disease was presumably coincidental.

DISCUSSION

As recently as 1961, Sheline, Goldberg, and Feldman, referring to external beam conventional radiation of the sella in acromegaly stated, 'subsequently, its value was proved and it remains the procedure of choice except in patients with large tumors... [requiring]... immediate decompression'.

Recent experience with objective criteria, including calcium, phosphorus, hydroxyproline, and carbohydrate metabolism, and biopsy of the costochondral junction justifies doubt as to the effectiveness of this level of radiation (Kozak *et al.*, 1966). Since the development of a reliable radioimmunoassay for growth hormone, several authors have investigated the effect of conventional external beam radiation on the plasma growth hormone levels in acromegaly (Beck *et al.*, 1965; Greenwood *et al.*, 1965; Roth *et al.*, 1967) and have failed to demonstrate a consistent or significant drop in the majority of their subjects.

Table I lists the previous conventional radiation therapy received by six of the 11 cases under study. They are not distinguished by either lower fasting growth hormone levels or greater susceptibility to subsequent interstitial radiation or cryosurgery. Indeed, the only case that did not respond satisfactorily to the interstitial application of 12,000 r at the gland margin (Case 7) received 4,475 r of external gamma radiation from a cobalt source, two and a half years previously.

Two cases (Case 5 and Case 7) were first seen before their radiation therapy. Fasting resting growth hormone levels were determined at that time. They were subsequently followed serially, at six month intervals, for over two years. There was no drop in growth hormone levels. This has also been our experience in a larger group of cases who have, as yet, not undergone stereotactic treatment.

On occasion, neurovascular damage (Peck and McGovern, 1966; Darmody, Thomas, and Gurdjian, 1967), sarcomas of the brain (Goldberg, Sheline, and Malamud, 1963; Waltz and Brownell, 1966), and carcinoma of the perinasal sinuses (Sheline *et al.*, 1961) have resulted from conventional therapy. In general, these cases have had as a single course, or more commonly as multiple courses, more than the

recommended dose of radiation, often over a shorter treatment period than is probably optimal in preventing complication. The report of Crompton and Layton (1961) on delayed fatal radionecrosis of the brain, including hypothalamus, in two cases, one receiving 4,500 r over four weeks and the other, 6,250 r over six weeks, reveals the potential although uncommon hazard of this form of therapy. Complications of conventional radiation therapy, although dramatic, must be rare. Nevertheless, we would consider interstitial radiation a superior form of therapy. It is possible to deliver a higher and controlled dose of radiation to the tumour and avoid significant radiation to the surrounding central nervous system.

Stereotactic interstitial radiation has been reported by others with variable success. Molinatti, Camanni, Massara, Olivetti, Pizzini, and Giuliani (1962), using free yttrium⁹⁰ pellets, reported clinical benefits and improvement in carbohydrate and calcium metabolism in 16 cases, only one of whom required replacement therapy for adrenal insufficiency. Two females had the return of menstruation and one male, return of potency. Growth hormone was not measured. One case had cerebrospinal fluid rhinorrhoea and paresis of the left oculomotor nerve, and one case had a temporary sixth nerve palsy and another transitory hemianopsia. Three cases had persistent polyuria. Total dose of radiation administered was 14.8 to 42 mc, or seven to 100 times the dose received in our series.

Hartog, Doyle, Fraser, and Joplin (1965) studied 22 patients receiving free interstitial implants of Au¹⁹⁸, Y⁹⁰, or both. The early cases were judged to have received 10,000 r at the tumour margin and this was later increased to an estimated 100,000 r. Nine of the patients had a second pituitary implant. Results, based on clinical findings and carbohydrate metabolism, were considered satisfactory in 13 of the 22 cases. Nine cases required replacement therapy due to pituitary insufficiency. One patient developed permanent diabetes insipidus. Growth hormone was not evaluated. A total of 39 implantations were performed in 28 patients (including six that were not fully evaluated post-operatively). Complications included eight cases of abscess within the sella turcica, four cases of cerebrospinal fluid rhinorrhoea, two cases of visual impairment, and one death.

Greenwood *et al.* (1965) report eight acromegalic subjects studied before and after Au¹⁹⁸ or Y⁹⁰ implantation of free seeds into the sella turcica, with a follow-up of several years in five patients. Their dose ranged from 6 to 70 mc in the yttrium⁹⁰ treated group with an estimated dose to the diaphragma sellae of 6 to 20,000 r. They considered

several of the patients to have vague clinical improvement but, measuring growth hormone, were unable to establish a clear-cut beneficial effect after their technique of therapy and concluded the dose of radiation used was inadequate to cause the symptoms of acromegaly to regress.

McCullagh, Feldstein, Tweed, and Dohn (1965) using the Forrest technique to fix yttrium⁹⁰ sources in the pituitary tumour of two acromegalic patients, report clinical improvement. Gelinas, McCullagh, and Dohn (1966), reporting from the same institution, describe a single case treated in a similar manner in which a slightly elevated fasting growth hormone level was reduced to normal. Kaufman, Pearson, Shealy, Chernak, Samaan, and Storaasli (1966) report the effects of interstitial radiation with fixed sources of yttrium⁹⁰ in nine cases of acromegaly. They used the Forrest technique of inserting the yttrium⁹⁰ tipped screws, which is more or less freehand under fluoroscopic control. Little effort was apparently expended in outlining the size and shape of the tumour. We would consider the dose of radiation used to be high, 2.8 to 36 mc. All nine cases had a drop in growth hormone levels but the three with the lowest growth hormone levels developed pituitary insufficiency. One case was judged to have had a remission in his acromegaly with retention of other pituitary functions. Complications were not mentioned.

Reviewing the above data in light of our experience, we conclude that lack of success in many of these cases was related to an uneven distribution of the radiation dose. Thus, even when sources over 200 times the strength of the sources used in this study were employed, a significant portion of the patients failed to have a clinical response. This would indicate that, either due to implantation technique or to migration of the source, significant portions of the tumour failed to receive adequate radiation. We also conclude that these higher doses of radiation are inadvisable, particularly if the source is allowed to migrate, for they can produce an unacceptable incidence of damage to surrounding neural structures and the pituitary remnant, and a high incidence of cerebrospinal fluid fistulae with attendant cerebrospinal fluid rhinorrhoea and intrasellar and intracranial infection.

Clinical improvement in a single case of acromegaly following cryogenic destruction of the adenoma was first reported in 1964 by Rand *et al.* Bleasel and Lazarus (1965) reported cryosurgery of four cases of acromegaly with one death. Clinical improvement occurred in the other cases. Wilson, Winternitz, Bertan, and Sizemore (1966) reported a single case with clinical improvement. We had the

opportunity to perform pre-operative and post-operative growth hormone levels on this patient in our laboratory. Pre-operative levels of 49 to 150 $\mu\text{g}/\text{ml}$. fell to less than 2 $\mu\text{g}/\text{ml}$. Wilson reports that this patient developed decreased pituitary function, however, and required cortisone replacement.

More recently, Dashe, Solomon, Rand, Frasier, Brown, and Spears (1966), reporting on six cases undergoing cryosurgery by a technique slightly different from that used in the present study, describe marked clinical improvement and partial or complete ablation of excess growth hormone levels in the peripheral blood. Two patients required replacement therapy, and only one had the optimal clinical result of complete ablation of excess growth hormone without pituitary insufficiency.

Adams, Seymour, Earll, Tuck, Sparks, and Forsham (1968) report the treatment of 16 acromegals. Multiple cryogenic lesions were placed in the sella turcica of these patients, using a smaller probe than that used in this study. Growth hormone was determined in 14 cases. The majority had a decrease in growth hormone levels. Ten of these consistently had growth hormone within normal limits for up to one year. Post-operatively, however, five cases required thyroid and three cortisone replacement, who did not require this before treatment. Four of six males developed decreased libido. These results are similar to our smaller series of acromegals treated with cryosurgery and confirm the usefulness of this form of therapy in ablating the excess growth hormone of acromegaly, but further emphasize the difficulty in predicting the critical level of cryodestruction needed for differential ablation of the pituitary adenoma with sparing of normal pituitary functions.

It is of concern that with either form of therapy adenoma cells may remain viable, multiply, and lead to recurrence of the tumour. To date, clinical, radiological, and endocrine studies have failed to reveal recrudescence, regardless of the method of therapy or the completeness of ablation.

SUMMARY

The trans-sphenoidal stereotactic treatment of 11 cases of acromegaly with growth hormone producing intrasellar tumours and proven elevated resting, fasting, growth hormone levels is presented. These were treated either with fixed sources of yttrium⁹⁰ or cryosurgery. The rationale for choice of treatment, technique used, and endocrine and clinical results are reported. It is concluded that interstitial fixed source radiation with yttrium⁹⁰ is an effective means of decreasing growth hormone levels and

arresting the clinical signs and symptoms of acromegaly, without adversely affecting other pituitary functions. At times, other pituitary functions are improved. With the authors' technique dosage of radiation 1/7 to 1/200 of conventional dosage is effective. Cryosurgery is an effective means of attacking tumours in which it is technically difficult to fix point sources of radiation. The critical parameters of cooling required to destroy the adenoma and preserve the normal pituitary remnant, however, are less predictable and differential pituitary preservation has been less well demonstrated.

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