METABOLIC CHANGES RESULTING FROM 90YT IRRADIATION OF THE PITUITARY IN A PATIENT WITH CUSHING'S SYNDROME

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SUMMARY

A detailed metabolic study has been made of a 48-year-old woman with Cushing's syndrome associated with presumed adrenocortical hyperplasia. The patient was shown to be secreting excessive amounts of cortisol. The urine contained low levels of aldosterone, but there was a hypokalaemic alkalosis. Plasma corticosterone was not raised.

 Destruction of the pituitary by insertion of 90Yt seeds produced clinical improvement and amelioration of hypertension. The adrenocortical activity promptly subsided to below normal levels. Negative nitrogen and calcium balances became positive, urine calcium fell and hypoglycaemia disappeared. The condition of hypokalaemic alkalosis was restored to normal and aldosterone excretion increased. The decline in thyroid activity was slower than that of adrenocortical activity. Calculation of the distribution of muscular and fatty tissue in the body showed that treatment produced an improvement. The significance of some of these changes is discussed.

It is widely believed that Cushing's syndrome, in cases where there is a hyperplastic state or condition of increased function of the adrenal cortex, is essentially due to increased secretion of corticotrophin by the pituitary. This may be sometimes demonstrated to be so [Clayton, 1958]. On this hypothesis a rational form of treatment in a suitable patient, for example a woman who has reached the age of the menopause, would be by destruction or removal of the anterior pituitary. This technique is widely used to suppress hormonal secretion in patients suffering from cancer of the breast, but so far has been infrequently applied in Cushing's syndrome. Surgical interference with the pituitary has been reported in two patients by Luft, Olivecrona, Ikkos & Hernberg [1957] who refer to the scanty earlier literature.

Although many of the metabolic abnormalities in patients with untreated Cushing's syndrome are widely known, detailed reports of these changes are infrequent (see Discussion). In addition to the better known abnormalities a few patients of this category with adrenal hyperplasia have been noted to have a condition of hypokalaemic alkalosis [Kepler, Sprague, Mason & Power, 1948; Sprague & Power, 1953], but again detailed hormonal studies in such patients are scarce.

For these reasons the present paper presents the findings, before and after treatment by pituitary ablation, in a patient with Cushing's syndrome in whom a condition of adrenal hyperplasia was inferred from the hormone investigations. It so happens that this patient exhibits also a condition of hypokalaemic alkalosis.
90YT IRRADIATION OF PITUITARY

METHODS

The analytical methods used are those given by Prunty, McSwiney & Hawkins [1959]. Aldosterone was estimated by the fluorescence technique of Brooks [1960]. Plasma-free cortisol and corticosterone were measured after paper chromatography by fluorescence. Plasma tetrahydrocortisol and tetrahydrocortisone glucuronides were similarly estimated after glucuronidase hydrolysis.

THE PATIENT

A woman aged 48 was admitted to St Thomas’s Hospital under the care of one of us (F.T.G.P.) with a 2 years’ history of Cushing’s syndrome. The clinical findings were quite typical of the condition, including moon face, purple abdominal striae, considerable obesity, thin abdominal skin, weakness and muscular wasting. There was X-ray evidence of moderate spinal osteoporosis, rib fractures, and osteoporosis of the skull. The last included an osteoporotic condition of the wall of the sella turcica which was confirmed during the surgical procedure. It was uncertain whether this appearance was entirely due to osteoporosis or to erosion by a basophil adenoma of the anterior pituitary.

Table 1. Treatment and blood-pressure values

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
<th>B.P. (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>Corticotrophin test</td>
<td>Days 1-3 and 11-36</td>
</tr>
<tr>
<td>4-7</td>
<td>90Yt implant to pituitary</td>
<td>160-230 (190 aver.)</td>
</tr>
<tr>
<td>11-36</td>
<td></td>
<td>100-170 (130 aver.)</td>
</tr>
<tr>
<td>37</td>
<td>90Yt implant to pituitary</td>
<td>150/95</td>
</tr>
<tr>
<td>38</td>
<td>Cortisone 75 mg, o.d.</td>
<td>170/120</td>
</tr>
<tr>
<td>39</td>
<td>Cortisone 50 mg, o.d.</td>
<td>100/80</td>
</tr>
<tr>
<td>40</td>
<td>Prednisone 10 mg, o.d.</td>
<td>150/110</td>
</tr>
<tr>
<td>41</td>
<td>Prednisone 5 mg, o.d.</td>
<td>165/115</td>
</tr>
<tr>
<td>54</td>
<td>Restricted Na intake (approx. 30 m-equiv.)</td>
<td>Thyroid gr. i (x2/day)</td>
</tr>
<tr>
<td>73</td>
<td></td>
<td>130/90</td>
</tr>
</tbody>
</table>

She was treated by paranasal implantation of 9 mc radioactive yttrium (90Yt), in the form of seeds, into the pituitary fossa. This produced considerable clinical improvement so that 1 year later she was much more energetic and well able to run her home which she had previously been unable to do. Soon after the implantation impairment of the visual fields in both temporal aspects was noted. This remained

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essentially unchanged. There was uncertainty whether this defect could have been caused by the radioactivity or was due to the presence of an adenoma. Other important details of treatment are given in Table 1.

**RESULTS**

**Hormone analysis**

The changes in urinary 17-oxosteroids and 17-oxogenic steroids are depicted in Fig. 1. It will be noted that there were considerable variations of the pre-treatment levels of both; 14–20 mg/day 17-oxosteroids, 11–40 mg/day 17-oxogenic steroids. The urine excretion of free cortisol was raised to 206 and 127 μg/day on two occasions (days 2 and 3). On the 2nd day after treatment 17-oxosteroids had fallen to 5 mg and 17-oxogenic steroids to 4 mg. The patient developed signs of adrenal crisis and treatment with cortisone had to be instituted. After changing to a small dose of prednisone on day 61, these steroids remained at low levels (1–2 mg/day and 2–4 mg/day, respectively). On re-admission 1 year later two attempts were made to withdraw the small dose of prednisone. However, on both attempts adrenal crises...
developed within a few hours of the patient receiving the last tablet and intravenous hydrocortisone hemisuccinate had to be administered urgently. It was therefore considered that the observed levels of 0-4–1.1 mg/day for 17-oxosteroids and 0–2.0 mg/day for 17-oxosteroids, over a 3-day period, approximated closely to the true adrenal contribution and were not significantly depressed by the small dose of prednisone being administered.

The patient's response to corticotrophin was tested by our standard procedure, namely the administration of 20 i.u. twice daily i.m. for 4 days [Prunty, 1956]. The same material was used for the pre- and postoperative tests (Table 2). As shown, the response was considerably reduced 1 year after operation. The marked preoperative response to corticotrophin was interpreted as evidence of the presence of adrenal hyperplasia.

Table 2. Responses to corticotrophin

<table>
<thead>
<tr>
<th>Before operation (day)</th>
<th>17-oxosteroids</th>
<th>17-oxogenic steroids</th>
<th>1 year postop.* (day)</th>
<th>17-oxosteroids</th>
<th>17-oxogenic steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>14-0</td>
<td>11-4</td>
<td>001</td>
<td>0-4</td>
<td>2-0</td>
</tr>
<tr>
<td>3</td>
<td>13-9</td>
<td>33-2</td>
<td>002</td>
<td>1-1</td>
<td>2-0</td>
</tr>
<tr>
<td>4</td>
<td>23-5</td>
<td>48-4</td>
<td>003</td>
<td>1-4</td>
<td>5-2</td>
</tr>
<tr>
<td>5</td>
<td>24-0</td>
<td>60-0</td>
<td>004</td>
<td>2-4</td>
<td>13-4</td>
</tr>
<tr>
<td>6†</td>
<td>35-0</td>
<td>83-0</td>
<td>005</td>
<td>5-0</td>
<td>18-1</td>
</tr>
<tr>
<td>7†</td>
<td>40-0</td>
<td>61-0</td>
<td>006</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>17-oxosteroids</td>
<td>17-oxogenic steroids</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patient receiving 5 mg prednisone daily.
† 20 i.u. Corticotropin (Armour, Batch 80205) i.m. twice daily.
Response in normal women, peak values: 17-oxosteroids 35.7 ± 0.9 s.e. mg/day; 17-oxogenic steroids 38.7 ± 6.9 mg/day [Prunty, Brooks & Mattingly, 1958].

Table 3. Excretion of aldosterone*

<table>
<thead>
<tr>
<th>Day</th>
<th>µg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1-1</td>
</tr>
<tr>
<td>3</td>
<td>1-1</td>
</tr>
<tr>
<td>4</td>
<td>1-9</td>
</tr>
<tr>
<td>42</td>
<td>0-9</td>
</tr>
<tr>
<td>93</td>
<td>3-5</td>
</tr>
<tr>
<td>After 1 year</td>
<td>4-0</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
</tr>
</tbody>
</table>

(Normal for bed patient 1–6 µg/day.)

* For treatment see Table 1.

Urinary aldosterone was measured on several occasions (Table 3). Initially, aldosterone excretion was low and higher values were obtained on day 93 and 1 year after operation. It should also be noted that in order to facilitate improvement in the patient's hypertension she was given a diet with a partially restricted salt intake (see Table 1).

Prior to treatment plasma-free cortisol was 11.5 µg/100 ml. on day 3 and 11.8 on day 4. Six hr after the injection of 20 i.u. corticotrophin i.m. on day 4 it had risen to 19.3 µg/100 ml. The amount of corticosterone in the plasma at these three times was not detectable and certainly not > 0.5 µg/100 ml. The corresponding values for
tetrahydrocortisol glucuronide and tetrahydrocortisone glucuronide were 1·5, 1·5, 3·0 and 0·8, 0·8 and 1·5 μg/100 ml. These compounds therefore formed an unusually small proportion of the plasma 17-hydroxycorticoids [Bongiovanni, 1954].

Thyroid function

The changes in plasma protein-bound iodine are shown in Fig. 1. It should be noted that this value was still 6·0 μg/100 ml. on day 68, but had fallen to 3·0 μg on day 90. It therefore fell at a much slower rate than the adrenal steroids. On day 18, the 24 hr uptake of 131I by the thyroid was 13%, and on day 58 it was 4%. Plasma cholesterol was 358 mg/100 ml. on day 25, 310 mg on day 53, 426 mg on day 91 and 459 mg 1 year after treatment. The B.M.R. at the last of these times was -22%.

Blood sugar levels

Prior to treatment the fasting blood sugar remained at hyperglycaemic levels (Fig. 1), and there was no ketosis. Following treatment it fell to normal levels. The apparent slight delay in this fall may be connected with the administration of the relatively large dose of 75 mg cortisone on day 40.

Nitrogen, calcium and phosphorus

Even on a high dietary intake of these three elements the patient was in negative balance (Fig. 2). This state was not significantly altered by a reduced intake necessitated by a reduction of potassium intake to 30 m-equiv. daily (see below). Nitrogen excretion was apparently not noticeably increased immediately following the mild surgical procedure; however, urinary calcium rose on days 39 and 40 to 351 and 402 mg/day and fell after replacement steroid therapy was instituted (Fig. 2). After treatment there was in general a definite improvement in nitrogen and calcium balance, so that after 1 year calcium balance had become positive and there was nitrogen equilibrium. It should be specially noted that not only did faecal calcium fall, but also urinary calcium. It is likely that the administration of corticotrophin (Table 2) during the penultimate period of calcium balance was in part, at least, instrumental in causing a rise in faecal calcium. The theoretical phosphorus balance calculated from nitrogen and calcium balances is indicated by the dotted line in Fig. 2. It will be seen that in general the phosphorus balance was that expected from the other two balances. Serum calcium, phosphorus and alkaline phosphatase were determined 1 year after and all found to be normal.

Electrolyte metabolism

Prior to treatment plasma values were as follows (m-equiv./l.): Na 137–143; K 2·9–3·4; CO₂ 38–41; Cl 88–89. There was, therefore, a condition of hypochloremic, hypokalaemic alkalosis. The serum sodium remained within normal limits throughout. The exchangeable 23Na and 42K were within normal limits prior to treatment, but the ratio 23Na/42K was raised above the normal of 0·9–1·0 (Table 4). Raising the intake (Fig. 3) to 230 m-equiv. before treatment did not lead to continued potassium retention, but a significant rise in the serum level to 4·8 m-equiv./l. occurred.
Restriction of K intake to 30 m-equiv./day resulted in continued loss of urinary K, even when serum K fell to 2-1 m-equiv./l. and there was a corresponding rise in CO₂. Postoperatively, elevation of K intake led to a continued retention of a total of 870 m-equiv. K with restitution of normal levels of serum K and CO₂. After 1 year on a normal diet, but restricted sodium intake, the serum levels remained normal. There was a reduction of 440 m-equiv. of exchangeable ²³Na and rise of 300 m-equiv.

Fig. 2. Balance of calcium, nitrogen and phosphorus before, immediately after, and 11 months after implantation of ⁹⁰Yt in the pituitary. In the case of urinary calcium, the results for individual days immediately before and after the implant are charted in separate blocks; all other results are on pooled samples.

⁴²K compared with preoperative levels (Table 4). The ratio ²³Na/⁴²K had then fallen to 1·23. At this time restriction of K intake again to 30 m-equiv. daily resulted in a fall of serum K to only 3·5 m-equiv./l. and there was no continued K loss in the urine (Fig. 4). It should be noted that prior to treatment faecal K excretion was also high and fell to a normal level later (Fig. 4).
**Renal function**

The patient prior to treatment had a voluntary urine volume of approx. 2·5 l./day, a mild polyuria. Creatinine clearance was 86 ml./min and after the injection of 5 u. pitressin tannate the urine osmolarity rose 817 m-osmole/l., i.e. just to normal levels. No attempt to observe changes in sodium balance in response to sodium restriction.

![Graph](Image)

**Fig. 3.** Cumulative potassium balance (m-equiv.), potassium intake (m-equiv./day), plasma potassium concentration (m-equiv./l.) and plasma bicarbonate concentration (m-equiv./l.).

**Table 4. Changes in lean body mass, and exchangeable sodium and potassium**

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>44 days after treatment</th>
<th>1 year after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea space (l.)</td>
<td>26·5</td>
<td>26·2</td>
<td>30·0</td>
</tr>
<tr>
<td>Total weight (kg)</td>
<td>71·9</td>
<td>70·2</td>
<td>68·3</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>36·3</td>
<td>35·9</td>
<td>41·1</td>
</tr>
<tr>
<td>Remaining weight (kg)</td>
<td>35·6</td>
<td>34·3</td>
<td>27·2</td>
</tr>
<tr>
<td>Total exchangeable $^{23}$Na (m-equiv.)</td>
<td>2660</td>
<td>—</td>
<td>2220</td>
</tr>
<tr>
<td>Total exchangeable $^{42}$K (m-equiv.)</td>
<td>1500</td>
<td>—</td>
<td>1800</td>
</tr>
<tr>
<td>$^{23}$Na/$^{42}$K</td>
<td>1·77</td>
<td>—</td>
<td>1·23</td>
</tr>
</tbody>
</table>
was made prior to operation, but the patient had been subjected to a sodium-restricted diet, in the management of her hypertension, prior to admission, without apparent ill effect. After operation, on days 73 onwards sodium intake was restricted to 24 m-equiv./day and she came into balance in 3 days. There was therefore no evidence of impairment of renal conservation of sodium.

Two days after 90Yt implantation the urine volume reached 7·8 l./day. It then rapidly settled to 5 l./day and by day 75 reached about 3·1 l./day. After 1 year it had fallen to 2·2 l./day.

![Graph showing plasma potassium and potassium balance before operation and 11 months afterwards.]

**Fig. 4.** Effect of low potassium intake (30 m-equiv./day) on plasma potassium and potassium balance before operation and 11 months afterwards.

**Changes in body composition**

These were calculated from the patient's weight and urea space values [Pace & Rathbun, 1945; McCance & Widdowson, 1951]. Prior to operation 'lean body mass' was 36·3 kg and 'remaining weight' 35·6 kg (Table 4). The ratio L.B.M./R.W. was therefore 1·0. A year after treatment lean body mass had risen by 4·8 kg and remaining weight fell by 8·4 kg. The ratio L.B.M./R.W. improved to 1·5.
DISCUSSION

The destruction of the pituitary of this patient by irradiation from $^{90}$Yt resulted in a considerable clinical improvement including a fall in blood pressure. This improvement was fully corroborated by the favourable changes in the biochemical findings. Although Albright [1942–43] strongly put forward the generally accepted view that the secretion of adrenal corticoid in excess (S hormone) led to nitrogen wastage in Cushing's syndrome, he had found it difficult in practice to demonstrate negative nitrogen balance in his three studies [see also Albright & Reifenstein, 1948]. Since then other investigators have proved more successful [Kepler et al. 1948; Henneman, Forbes, Raker & Albright, 1954; Tuttle & Figueroa, 1958; Mason, Richardson & King, 1958]. The first two of these studies concerned cases of adrenal carcinoma and adenoma, respectively. All are agreed that removal of the tumour or adrenalectomy results in restoration of positive nitrogen balance. This is also achieved in the present instance by depression of pituitary activity.

The output of corticoid metabolites in the urine (17-oxogenic steroids) was extremely variable prior to operation. This variability is in accordance with earlier findings [Prunty, 1956] and with observations of others [Birke, Plantin & Diczfalusy, 1956; Bayliss, 1957]. The level of corticotrophin in the blood was not high enough to reach detectable levels by the method used (Clayton [1958], patient D), but may nevertheless still have been above normal. That the pituitary activity and presumably also corticotrophin production was in fact greatly reduced, if not abolished entirely, is suggested by the dramatic fall in urine 17-oxosteroid and 17-oxogenic steroid excretion, and the great sensitivity of the patient to withdrawal of small amounts of replacement therapy. The reduced response of the adrenal to stimulation with exogenous corticotrophin also supports this belief. Whilst the fall in these steroids was almost precipitous, the expected fall in thyroid function appeared to be much delayed, but ultimately some clinical evidence of myxoedema appeared with insufficient thyroid replacement therapy. The low level of aldosterone excretion prior to operation rose as the patient improved. The probable contribution of the sodium restriction to the stimulation of this rise must be acknowledged, but nevertheless the independence of aldosterone production from pituitary function is once more exemplified [Farrell, 1958].

The rapid fall off in pituitary function was accompanied by early changes in the other parameters. Blood sugar levels fell rapidly. It has been noted that the delayed fall on day 40 may well have been related to the high dosage of cortisone given at this time. Nitrogen balance quickly became positive, the balance of calcium also rapidly improved and was positive 1 year later. This change was accompanied by fall of both faecal and urinary calcium. It seems that adreno-corticoids have some antagonistic action to vitamin D [Anderson, Dent, Harper & Philpot, 1954; McSwiney & Mills, 1956], and this is the probable reason for the improvement in the faecal calcium. The usual effect of these hormones on patients with normal adrenals is to cause an increase in urinary calcium [McSwiney & Mills, 1956; Henneman, Irwin, Wang & Burrage, 1955], presumably by decreasing tubular reabsorption of calcium. The removal of the excess corticoid secretion in this case would be expected therefore to reduce urinary calcium, as also happened in the
patients of Henneman et al. [1954] and Tuttle & Figueroa [1958]. Nevertheless, there was pronounced hypercalcuria for 2 days after operation, which decreased with the institution of corticoid replacement therapy. It also appears from the report of Henneman et al. [1954] and Tuttle & Figueroa [1958] that there may be an optimum replacement level for corticoid to bring about a sustained decrease of urine calcium.

The reason for the development of hypokalaemic alkalosis in some patients with Cushing's syndrome is not entirely understood. The excretion of aldosterone in this patient was low, and increased amounts of another substance with pronounced mineralocorticoid action, namely corticosterone, could not be demonstrated in the plasma. Judging by the few reports of aldosterone excretion in the urine of such patients with adrenal hyperplasia as distinct from those with tumours, normal or low levels are often to be expected, even if hypokalaemia is present [Hernando, Crabbé, Ross, Reddy, Renold, Nelson & Thorn, 1957; Beaulieu, de Vigan & Jayle, 1958]. We have made a similar finding in a patient reported by Edmunds, McKeown & Coleman [1958]. The behaviour of the present patient to dietary potassium restriction was the same as in instances where the hypokalaemic alkalosis might reasonably be ascribed to excess secretion of aldosterone [Brooks, McSwiney, Prunty & Wood, 1957]. It should also be noted that the potassium depletion did not result in this instance in pronounced renal impairment with isosthenuria. After treatment the patient's response to deprivation was restored to normal, her potassium deficit was repleted and the hypokalaemia and alkalosis were corrected. On account of the wide range of normal values for the exchangeable $^{23}$Na and $^{42}$K, expression of these as the ratio $^{23}$Na/$^{42}$K is preferable in the detection of an abnormality and its improvement in these circumstances [Arons, Nusimovich, Vanderlinde & Thorn, 1958].

The changes in estimated body composition are a striking objective means of showing restoration towards normal. There was an absolute increase in the lean body mass, and not only a fall of weight due to reduction of the 'remaining weight' fraction which is of course largely made up of the contribution of fat. The increase in $^{42}$K space is about that expected from the estimated increase in lean body mass, and this, therefore, leads to the conclusion, that even in the presence of the hypokalaemia the potassium content per unit weight of muscle tissue was not greatly reduced.

A few data from the study of this patient have been reported at a recent conference [Prunty, 1959: Case I]. We are indebted to Dr J. S. Richardson for referring this case for study and treatment, and to Mr G. H. Bateman for insertion of the $^{90}$Yt seeds.

REFERENCES

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