TREATMENT OF CUSHING'S DISEASE
BY PITUITARY SURGERY. REPORT OF TWO CASES

By
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The first attempt to treat Cushing’s disease\(^1\) by pituitary surgery was made by Naffziger who, in 1933, performed a hypophysectomy on a patient with this condition. Histological examination of the tissue removed revealed a pituitary adenoma of uncertain type. The patient improved dramatically after the operation and remained in remission during the first postoperative year. After this period the clinical syndrome reappeared; the patient died from the disease seven years after the operation. Post-mortem examination was not performed (Lisser, 1944). However, the clinical picture and, particularly, the reappearance of menstruation postoperatively demonstrates that the hypophysectomy was not complete.

Pattison & Swan (1938) implanted radon seeds into the hypophysis of patients with Cushing’s disease, and obtained improvement. This procedure was repeated by Northfield (1949) in four patients. The clinical picture of the disease disappeared (follow-up study for 9 years) in a patient in whom a pituitary adenoma was present.

Report of a case of Cushing’s disease successfully treated by electrocoagulation of the hypophysis was presented from our department in 1953 (Arner et al., 1953). In the present paper a 5-year follow-up study of this case is presented. Moreover another case of Cushing’s disease, successfully treated by hypophysectomy is recorded.

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1. The term »Cushing’s disease« is used here to designate those cases of »Cushing’s syndrome«, which are not due to adrenocortical tumour.
**CASE REPORTS**

First case.

A female born 1927 presented at the age of 15 (1942) the clinical picture of Cushing's syndrome. X-ray studies of the adrenals after perirenal insufflation and palpation of the adrenals during exploratory laparotomy in 1943 gave normal findings. Two courses of X-ray irradiation to the hypophysis were given in July and November 1943 (1500 r in each). A rapid improvement followed shortly after the first of these, and the patient remained in remission up to the spring of 1948. The syndrome then reappeared and progressed continuously. X-ray treatment of the hypophysis in September 1948 induced only slight temporary improvement. Similar treatment in April 1950 (4500 r) was without effect. At examination in May 1951 she presented a typical Cushing's syndrome. Her appearance is shown in Fig. 1a. There was marked obesity (height 155 cm., weight 70 kg.) of the buffalo type, fullmoon face, hypertrichosis, acne, purple striae, echymoses, thin dry skin, pronounced thoracic kyphosis and a cervicodorsal fat pad. The blood pressure was 170–200/120–135. Laboratory examinations showed increased values for urinary corticoids, a pathological glucose tolerance test and lymphopenia (Table 1).

Electrocoagulation of the pituitary gland was performed twice, on June 26 and July 6, 1951. Substitution therapy was not given after the operation. A rapid subjective and objective improvement was noticed postoperatively. In October 1952 no

<table>
<thead>
<tr>
<th></th>
<th>Before operation</th>
<th>After operation</th>
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<tbody>
<tr>
<td></td>
<td>May 1951</td>
<td>October 1952</td>
</tr>
<tr>
<td>body weight (kg.)</td>
<td>70</td>
<td>49</td>
</tr>
<tr>
<td>blood pressure (mm. Hg.)</td>
<td>170–200/120–135</td>
<td>120/75</td>
</tr>
<tr>
<td>heart size (cm.$^3$/sq. m. surface area)</td>
<td>460</td>
<td>310</td>
</tr>
<tr>
<td>urinary corticoids (mg./24 hrs.)</td>
<td>1.7–3.7$^1$</td>
<td>0.9–1.5$^1$</td>
</tr>
<tr>
<td>17-ketosteroids (mg./24 hrs.)</td>
<td>7–12</td>
<td>3–4</td>
</tr>
<tr>
<td>circulating eosinophils (per mm.$^3$)</td>
<td>86</td>
<td>357</td>
</tr>
<tr>
<td>diff. count: eosinophils/lymphocytes (%)</td>
<td>0–1/6–10</td>
<td>10/39</td>
</tr>
<tr>
<td>cholesterol (mg. %/)</td>
<td>270</td>
<td>250</td>
</tr>
<tr>
<td>BMR (%/o)</td>
<td>-12</td>
<td>+4</td>
</tr>
<tr>
<td>I$^{131}$-test: 24 hrs. uptake (%/o) / thyroid clearance$^4$ (ml./min.)</td>
<td>amenorrhea</td>
<td>pregnant</td>
</tr>
<tr>
<td>menstruation</td>
<td>normal</td>
<td></td>
</tr>
</tbody>
</table>

1. measured according to Sprecher (1950); normal values 1.0–1.5 mg.
2. measured according to Norymberski et al. (1953).
3. oral two-dose, one hour test.
4. according to Berson et al. (1952).
Case 1.  
A. In May 1951; before electrocoagulation of hypophysis.  
B. In September 1952.  
C. In January 1956.

symptoms or signs of her previous disease were present (Table 1). Menstruations re- 
appeared three weeks after the second operation, and the patient became pregnant in 
August 1952. The pregnancy was artificially terminated in December 1952, and the 
menstruations reappeared in January 1953. The function of the thyroid and adrenals 
was found to be normal postoperatively (for details see Arner et al., 1953).

The patient was reexamined for the last time in January 1956, four and a half years 
after the operation. During the last three years she had been in perfect health and 
working normally. She was free of any symptoms. Her appearance (Fig. 1 c) was that 
of a healthy young female. The body weight was 45 kg.; she had thus lost 25 kg. after 
the operation. Signs of Cushing's syndrome were completely absent, the only re- 
mainring signs of her previous disease being a thoracic kyphosis and pale atrophic
striae. Blood pressure and heart size were within normal limits. The daily urinary excretion of corticoids and 17-ketosteroids was normal. Gonadal and thyroidal functions were normal. She had normal menstruations. Symptoms of hypothyroidism were absent. Blood cholesterol, BMR and $^{131}$-values were within normal limits (Table 1). No substitution therapy was given after the operation.

**Second case.**

Unmarried male from Finland, born 1934. Cushing's syndrome seems to have started in 1951, when the patient noticed rounding of the face and a rapid increase in body weight (10 kg. in one months). Headache and back pain appeared and also purplish striae.

At examination in June 1952 he had a fullblown Cushing's syndrome with fullmoon face, typical obesity with a cervicodorsal fat pad (body weight 85 kg., height 176 cm.), purple striae, blood pressure 150/105, decreased dextrose tolerance and eosinopenia. The excretion of 17-ketosteroids was 19.2 and of corticoids 2.1 mg. (normal value less than 1.0 mg.) in 24 hours. Subtotal adrenalectomy was performed on July 3 and September 15, 1952. Small remnants were left from both adrenals. They were definitely enlarged, the excised parts of the adrenals weighing 18 and 19.5 gm. After the initial postoperative period the substitution therapy consisted of 12.5 mg. of cortisone per day.

Cushing's syndrome disappeared postoperatively, and the patient remained in remission up to August 1954, i.e. for two years. His body weight decreased to 70 kg., the striae become more pale, the systolic blood pressure stayed at 115 mm. Hg. Urinary 17-ketosteroids were 3 mg./24 hrs. three weeks after the last operation.

Signs of adrenocortical hyperfunction reappeared in September 1954. The disease progressed rapidly and by December 1954 the condition of the patient was that of a pronounced Cushing's syndrome. Body weight increased by 8 kg. in three months, the blood pressure increased to 170/110 mm.Hg.; the excretion of 17-ketosteroids was 14 mg. and of corticoids 2.4 mg. per day. Reoperation on the adrenals was considered as being very difficult by the attending surgeon and the patient was therefore given X-ray irradiation to the pituitary gland in January 1955. Despite this, his disease progressed continuously. His appearance in April 1955 is shown in Fig. 2 a. He presented a typical fullmoon face of a bluish red colour, buffal0 type obesity (height 178 cm. weight 98 kg.), a cervicodorsal fat pad, slight thoracic kyphosis, acne, purplish striae and a dry atrophic skin. His principal complains were tiredness, incapacity of mental concentration, pains in the vertebral column, exertional dyspnoea and decreased libido. His blood pressure was 170/80 mm.Hg. The skull was radiographically normal. Urinary corticoids varied between 10–61 mg. and 17-ketosteroids between 10–28 mg./24 hrs. Circulating eosinophils were only 3/mm.$^3$; in the differential count the lymphocytes varied between 12–22 %, and red blood cells were 3.8–4.1 mill./mm.$^3$. Glucose tolerance tests (intravenous and oral) were abnormal, and he was insulin resistant.

**Hypophysectomy was performed on April 20, 1954** by a frontotemporal approach. In order to study the hormonal changes postoperatively, it was decided to operate without previous or simultaneous administration of adrenocortical hormones, and to keep the patient as long as possible without substitution therapy. However, the blood pressure dropped suddenly to 80 mm. a few hours after the operation, and therefore substitution with cortisone$^3$ and desoxycorticosterone was started. The electrocardiogram demon-

2. According to Norymberski et al. (1953).
3. The generous supply of steroid hormones by Ciba Produkter, A.B., Stockholm, is gratefully acknowledged.
Case 2. 
A. In April 1955, before hypophysectomy.
B. In September 1955.
C. In January 1956.

Fig. 2.

strated a cardiac infarct, which was treated by the conventional methods. The patient left the hospital in the middle of June 1955, two months after the operation. During this two months period the substitution therapy consisted only of cortisone, 37.5 mg./day. After the second postoperative week there was a pronounced change in the colour of the skin and striae, which became pale. It is of interest that the change in the colour of the striae was regional, and one could see pale areas within the purplish striae. Moreover, there was a pronounced peeling of the skin as in the case of scarlet fever. In June 1955 the patient had a myxoedematous appearance. The BMR was −38%, blood cholesterol 428 mg./%. Radioidine test gave very low values: 24 hrs uptake 5%.

4. According to Berson et al. (1952).
thyroidal clearance 7 ml/min. On 37.5 mg. cortisone daily he excreted 0–1.7 mg. of 17-ketosteroids and 9–12 mg. of corticoids per 24 hrs., and the circulating eosinophils varied between 126 and 275 per cmm. He was sent home on a substitution of cortisone (37.5 mg.), and thyroid in a dose corresponding to 150 micrograms of thyroxine.

When examined again in September 1955, he was much better. He was free of any symptoms except for decreased libido and decreased growth of the facial hair. His appearance which is shown in Fig. 2 b, had changed profoundly. His body weight had decreased by 10 kg. There remained large atrophic striae, but they were now pale (not seen in Fig. 2). Full-moon face, facial rubecosis, buffalo-type obesity, acne and dry skin were absent. The testicles were small and soft; the prostate was hardly palpable. The substitution therapy was continued as previously with the addition of androgens (implantation of 500 mg. of testosterone propionate in September 1955).

The patient was last seen in May 1956. He was free of any symptoms and was working normally. His appearance was that of a normal young male, except for large pale atrophic striae. Signs of Cushing’s syndrome were absent. The blood pressure was 110/80 mm.Hg. He left the hospital with the same substitution therapy as before but with the addition of Triolandren (Ciba) and an increase in the daily cortisone dosage to 50 mg.

**DISCUSSION**

The mechanism by which electrocoagulation of the hypophysis induced the disappearance of the disease in the first case is not clear. The destruction of the pituitary tissue was far from complete, as demonstrated by the normal function of the thyroid, gonads and adrenal cortex after the operation. Moreover, the fact that the patient became pregnant demonstrates that she had enough functional reserves in her pituitary gland. A reasonable explanation would be that, by chance, a pituitary adenoma was destroyed by the electrocoagulation, this adenoma being responsible for the hyperfunction of the adrenal cortices. An analogous case was reported by Northfield (1949): radon implantation in the hypophysis of a patient with Cushing’s syndrome resulted in the disappearance of the disease, the patient retaining normal function of the peripheral endocrine glands postoperatively. Histological examination of pituitary tissue in connection with the operation revealed a pituitary adenoma. The possibility that electrocoagulation caused the disappearance of the disease by a simple reduction of the pituitary tissue seems less probable.

The situation is clearer in the second case. After the hypophysectomy, there was a pronounced decrease in the function of the thyroid and testes. Adrenocortical function could not be studied, since the patient was continuously on cortisone substitution therapy. However, in addition to the disappearance of Cushing’s syndrome, there was a pronounced decrease in the urinary excretion of steroid metabolites, although the patient was receiving cortisone. The values for 17-ketosteroids and corticoids in the urine correspond to those expected from the exogenous cortisone as found by us after hypophysectomy in cancer patients. Therefore it seems very probable that, in this case, the hypophysectomy was complete – at least from a functional point of view. Consequently, the
disappearance of Cushing’s syndrome in this patient should be attributed to the elimination of the pituitary function.

The pronounced fall in blood pressure in this case during the operation day could obviously be attributed to the infarction of the heart. It is, however, very probable that the shock was due to adrenocortical insufficiency, and that the infarction was secondary to the fall in blood pressure. It has been demonstrated that in man, half an hour after section of the pituitary stalk, measurable amounts of corticotrophin cannot be demonstrated in the plasma (Matson, 1956).

The question whether Cushing’s disease is of pituitary or adrenocortical origin has been widely discussed (Albright, 1943, Kepler, 1941, Soffer, 1951, Sprague, 1955, Gordon, 1956). The result in our first case suggests that, in this patient, Cushing’s disease was of pituitary origin. As to the second case no statement is possible, since »one can also regard the influence of the pituitary body in the pathogenesis of Cushing’s syndrome as a condition necessary to its production rather than as a primary etiological factor« (Kepler, 1949). In this connection, it should be mentioned that the sensitivity of the adrenal cortex to stimulation by corticotrophin has been found to be increased in patients with Cushing’s disease (Grumbach et al., 1955). Nevertheless, the results in the second case demonstrate that hypophysectomy should be considered in those cases of Cushing’s disease in which adrenocortical surgery is considered undesirable for various reasons.

SUMMARY

Electrocoagulation of the hypophysis in one case and hypophysectomy in a second case of Cushing’s disease resulted in a complete disappearance of the disease.

REFERENCES

Albright, F.: Harvey Lectures 38, 123, 1942–43.