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SURGICAL TREATMENT OF CUSHING'S DISEASE CAUSED BY ADRENOCORTICAL HYPERPLASIA: EXPERIENCES WITH BILATERAL ADRENALECTOMY

By

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Experience with the surgical treatment of hypercorticism caused by bilateral adrenocortical hyperplasia in 16 patients is discussed. The treatment of choice is bilateral total adrenalectomy. Following subtotal adrenalectomy recurrence occurred in three of six patients; a third operation was needed in two cases, while permanent hypadrenia developed in the third. There was no operative mortality. One patient died 9 years after surgery, but the death was not related to the original disease. The clinical symptoms of hypercorticism subsided in every totally adrenalectomized patient. Indication and contraindication of adrenalectomy, the surgical method, and the problems of pre- and postoperative treatment are discussed.

Introduction

The first successful adrenalectomy in man was performed by the London surgeon THORNTON in 1889 [55]. Later, the operation was carried out only sporadically because of the frequently fatal hypoadrenalism developing in the postoperative period. According to GOLDENBERG [14], before 1927 only five successful operations were recorded. With the improvement of diagnostics and the surgical technique, and with the availability of effective hormone preparations, adrenalectomy has become more frequent during the past 20 years.

Bilateral subtotal adrenalectomy was considered to be a suitable cure of Cushing's disease due to hyperplasia [3, 26, 52]. SOFFER et al. [49] observed that unilateral adrenalectomy combined with X-ray irradiation of the pituitary region also induced a satisfactory remission. Depending on the severity of the disease, other authors [38, 46] applied various surgical solutions (unilateral total, bilateral subtotal, and bilateral total adrenalectomy). In recent years, bilateral total adrenalectomy has been considered the method of choice [7, 11, 12, 22, 34, 35, 43, 57].

In 1968 we reported on the surgical treatment of adrenal diseases associated with enhanced hormone production [37]. At that time our material included only four cases of bilateral total adrenalectomy. Our experience with

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adrenalectomy has since accumulated considerably, and we felt that the treatment of Cushing's disease caused by bilateral adrenocortical hyperplasia should be reconsidered on the basis of our own data.

Patients

In the period 1958 to 1973, bilateral adrenalectomy was carried out on 16 patients with Cushing's disease caused by adrenocortical hyperplasia. During the fifteen years, both the diagnostic and the therapeutic procedures underwent several modifications. Pre- and postoperative examination of the patients was performed at the First Department of Medicine. In patients 1, 6 and 7 unilateral adrenalectomy was carried out in Budapest, while all other operations took place at the First Department of Surgery in Szeged.

Diagnostic procedures

The following parameters were determined: body height, body weight, blood pressure, neutral total 17-ketosteroid and total 17α-hydroxycorticosteroid excretion, serum cortisol level, blood sugar, blood sugar curve after oral glucose loading, serum sodium, potassium, cholesterol, creatinine and non-protein nitrogen levels, and endogenous creatinine clearance.

Total urinary 17-ketosteroid content was determined by the procedure of HOLTORFF and KOCH [16] as modified by FAREDIN et al. [8], and total 17α-hydroxycorticosteroid excretion (Porter—Silber chromogens) by the method of FAREDIN and TÓTH [9]. Urine was collected on three consecutive days. In the tables the average 24-hour steroid excretion is shown. ACTH suppression was examined by administering 0.5 mg dexamethasone (Oradexon, Organon) in 6-hour intervals for 6 days, and steroid excretion was determined in urine collected on the 4th, 5th and 6th days. If the decrease of hormone excretion did not reach 50% of the initial value, the above procedure was repeated with a 2.0 mg dose of dexamethasone. In the first five patients ACTH suppression was carried out with 5 mg prednisolone given every 6 hours.

The serum cortisol level was determined by MATTINGLY's modification [29] of the method of SPENCER-PEET et al. [51], with an Opton spectrofluorimeter. Blood samples were taken at 8, 14, 20 and 2 o'clock. The two extreme values are shown to illustrate the daily cortisol rhythm. The overnight test was used to examine ACTH suppression: 1.0 mg dexamethasone was administered orally at midnight, and the serum cortisol level was determined in a sample taken at 8 a.m. next morning. In the cases observed before 1965, the serum cortisol level was not determined.

Clinical symptoms and laboratory data

The main clinical data observed before the operation are listed in Table I. Of the 16 patients, 11 were female, and 5 male. Their age ranged from 10 to 45 years. In three cases (patients 12, 13 and 14) the diagnosis was juvenile Cushing's disease associated with retarded growth; the epiphyseal fugae were open, but in Case 14 signs of early puberty were observed. The majority of the patients exhibited various degrees of obesity and hypertension, associated with hirsutism and menstrual disorders in the females. Osteoporosis was observed in some patients, and signs of cardiac insufficiency in others.

As regards the laboratory data (Table II), total 17-ketosteroid and hydroxycorticosteroid excretion was enhanced in most patients; there was no daily fluctuation in the serum cortisol level, and steroid excretion and the serum cortisol level could not be suppressed with a small dose of dexamethasone.

Table I

No.	Name and sex	No. of operation	Age, years	Duration of disease, years	Main clinical symptoms	Body height, cm	Body weight, kg	Blood pressure, mm Hg
1	N. Zs.	I	24	1	Menstrual disturbance, obesity,			
	F	II	29	6	hypertension	177	83	170/90
		III	31	8			81	130/90
2	L. A.	I	26	2	Obesity, striae, hirsutism, hyper-	168	80	175/100
	F	II	28	4	tension		76	180/120
3	D. E.	I	25	8	Hirsutism, obesity, striae	154	93	150/90
	F	II	25	8			91	140/85
4	M. S.	I	25	2	Obesity, striae, hypertension,	161	83	190/120
	F	II	25	2	hirsutism, menstrual disturbance		85	200/125
5	P. T.	I	36	4	Obesity, hypertension	162	82	180/110
	F	II	39	7	+ osteoporosis		76	190/120
6	Cs. L.	I	27	3	Obesity, striae, hirsutism,	153		
	F	II	29	5	amenorrhoea + osteoporosis,		60	170/120
		III	38	14	cutaneous atrophy		63	190/110
7	L. J.	I	44	3	Amenorrhoea, obesity, striae,	158		
	F	II	45	4	hirsutism, adynamia, hypertension		69	220/110
8	F. Z.	I	38	4	Obesity, striae, hypertension,	165	76	190/130
	M	II	38	4	cardiac insufficiency, adynamia		73	180/120
9	Cs. K.	I	22	3	Amenorrhoea, obesity, striae,	162	91	170/105
	F	II	22	3	hirsutism, hypertension		89	160/100
10	V. S.	I	33	6	Obesity, striae, cardiac insuffi-	166	93	220/150
	M	II	33	6	ciency, hypertension, angina,		83	215/130
					diabetes mellitus			
11	G. L.	I	36	1	Menstrual disturbance, obesity,	158	73	160/100
	F	II	36	1	striae, hirsutism, hypertension		73	150/100
12	V. G.	I	13	6	Small growth, obesity, striae,	134	44	140/85
	F	II	13	6	hirsutism	134	42	120/85
13	H. D.	I	16	3	Small growth, obesity, hyper-	138	42	160/100
	M	II	16	3	tension	139	41	120/80
14	F. J.	I	10	4	Small growth, obesity, premature	131	50	120/80
	M	II	10	4	puberty	133	50	120/80
15	L. A.	I	36	9	Obesity, hypertension, hirsutism,	158	99	160/100
	F	II	36	9	diabetes mellitus, osteoporosis		99	180/110
16	V. F.	I	14	3	Obesity, striae	160	67	140/90
	M	II	15	4			79	130/80

Table II

No.	No. of operation	17-ketosteroids excretion (mg/24 h)		Corticoids excretion (mg/24 h)		Se. cortisol μg/100 ml		Glucose tolerance	Se. K mEq/l	Se. Na mEq/l
		No treatment	After suppress.	No treatment	After suppress.	Rhythm.	Ora-dexone			
1	II	23	19	12	13			N	3.7	135
	III	27	14	16	14			N	4.9	137
2	I	25	23	5	4			D	4.1	140
	II	15	18	15	14			N	4.0	139
3	I	15	12	4	5			N	4.2	138
	II	18	13	11	7			N	4.1	141
4	I	27	21	9	9			N	3.9	137
	II	5	—	0.7	—			N	4.7	135
5	I	37	27	18	13			D	3.6	138
	II	26	17	12	8			N	3.3	144
6	I	16	—	5	—			D		
	II	16	15	4	7			D	3.8	142
	III	11	9	7	4	21—19	22	N	4.3	134
7	II	20	16	10	7	28—20	22	D	4.9	150
8	I	22	16	18	13	27—26	20	D	2.9	148
	II	20	16	8	9	24—20	21		4.2	145
9	I	41	33	16	9	32—28	26	N	2.5	149
	II	23	15	15	9	29—25	24	N	4.0	144
10	I	41	9	29	4	28—20	23	MD	3.5	138
	II	21	8	17	3	27—21	20	D	5.2	140
11	I	19	17	12	11	24—15	19	D	4.3	139
	II	8	6	8	7	18—14	16	D	4.6	140
12	I	8	5	8	3	19—12	15	N	5.8	149
	II	7	3	5	2	19—14	15	N	5.5	148
13	I	19	5	12	2	21—11	6	N	5.0	135
	II	15	6	6	3	18—10	7	N	3.9	138
14	I	10	2	12	0.6	15—10	4	N	4.7	137
	II	10	3	11	2	20—18	5	N	4.2	142
15	I	11	11	10	6	27—19	22	MD	4.2	135
	II	8	5	12	7	23—19	20	D	4.6	138
16	I	30	24	24	16	29—24	26	N	4.1	141
	II	24	27	16	18	26—23	25	N	4.2	133

Glucose tolerance N: normal
D: decreased
MD: manifest diabetes

Unilateral adrenalectomy had practically no effect on adrenocortical function. Glucose tolerance was decreased in eight patients, and four had hypokalaemia.

The laboratory results were important not only in view of their diagnostic value but also because they had a substantial influence on preoperative treatment. Tomography of the adrenal region was carried out after presacral insufflation in all patients before surgery, but the presence of a tumour could not be confirmed in a single case. Recently more modern procedures have been introduced (adrenal venography, arteriography, isolated hormone sampling, adrenal scintigraphy with ^{131}I-cholesterol). Naturally, the method of presacral insufflation (as a consequence of its disadvantages) has lost much of its practical value.

Table III shows the preoperative treatment, the postoperative complications and treatment, and the histological findings.

Preoperative treatment

Apart from X-ray irradiation (4000—6000 R) of the hypophyseal region, no special treatment was given before the first intervention. Only those patients were subjected to operation in whom radiation therapy failed to bring about remission. In the younger patients even hypophyseal irradiation was omitted. Stabilization of the cardiac state was considered of importance. In the event of hypokalaemia, potassium and spironolactone (Aldactone, Searle) were administered. On the evening before the second operation 50—100 mg hydrocortisone (Hydroadreson, Organon) or cortisone acetate (Adreson, Organon) was given intramuscularly. This dose was repeated in the morning before the operation, and in most cases the therapy was supplemented with desoxycortone (5 mg Decosteron, Richter Co., Budapest).

Operative technique

With the exception of one case (patient 8), the operation was performed in a few early cases through a lumbar incision and more recently exclusively by means of a transthoracic-transdiaphragmatic approach through the 9th intercostal space. This latter affords very good access, and has proved advantageous with regard to early ambulation and uneventful wound healing. The procedure demands some skill in thoracic surgery, but the transabdominal approach too may be difficult because of the common obesity.

The adrenals were removed in two stages. In the first period, up to 1965, mainly subtotal adrenalectomy and subtotal adrenalectomy on the other side were performed. Subsequently, a third operation had to be done because of recurrence. In two cases (patients 3 and 4) the adrenalectomy was subtotal on both sides, while in patients 2 and 5 it was subtotal on one side and total on the other. In patients 7—16 bilateral total adrenalectomy was carried out.

Complications and postoperative treatment

Immediately after the first operation, hypotension was observed in patient 2 and temporary jaundice in patient 11. In patient 1 a minor abscess developed in the operative area. In the other patients, the first stage of adrenalectomy was not accompanied by any postoperative complication. Accordingly, special hormone treatment was not continued after the first operation; only a few patients were treated with cortisone preparations for a short time. Following the removal of the second adrenal, there were changes in blood pressure. Hypotension or blood pressure fluctuations were observed in half of the patients, with a typical hypadrenic crisis in one case (patient 1, after the third operation), and hypertension

Table III

No.	No. of operation	Preoperative treatment	Surgery	Adrenalectomy	Postoperative complication and treatment	Adrenal weight (g)	Histology
1	I	Hypophyseal X-ray	Lumbar	L.H.S. tot. Budapest	L.H.S. epinephr. abscess		
	II	Cortisone, Hypophyseal X-ray, Potassium	Lumbar	R.H.S. subtot.	Hypotension, Cortisone		Diffuse hyperplasia
	III	Cortisone, Desoxycortone	Transdiaphragmatic	R.H.S. tot.	Hypadrenic crisis, Cortisone, DOCA, Noradrenaline		Diffuse hyperplasia
2	I	—	Lumbar	R.H.S. subtot.	Hypotension, Noradrenaline, Cortisone		Diffuse hyperplasia
	II	Hypophyseal X-ray	Lumbar	L.H.S. tot.	Tension fluctuation, Cortisone, DOCA,	8.7	Diffuse hyperplasia
3	I	—	Lumbar	R.H.S. subtot.	Good general state		Adenomatous hyperplasia
	II	Prednisolone, Desoxycortone	Lumbar	L.H.S. subtot.	Hypotension, DOCA, Cortisone		Diffuse hyperplasia
4	I	Hypophyseal X-ray	Lumbar	L.H.S. subtot.	Normal conditions		Diffuse hyperplasia
	II	Cortisone, Desoxycortone	Lumbar	R.H.S. subtot.	Hypotension, DOCA, Cortisone		Normal
5	I	Hypophyseal X-ray, Potassium, Spironolactone	Lumbar	L.H.S. subtot.	Normal conditions		Z. reticularis, hyperplasia
	II	Digitalis, Spironolactone, Desoxycortone	Transdiaphragmatic	R.H.S. tot.	Tension fluctuation, pneumothorax, pneumonia, Cortisone	10.2	Adenomatous hyperplasia

6	I	—	Lumbar	L.H.S. subtot. Budapest	Good general condition		Diffuse hyperplasia
	II	Hypophyseal X-ray Cortisone	Lumbar	R.H.S. tot.	Hypotension, Cortisone, DOCA	9.7	Diffuse hyperplasia
	III	Cortisone Desoxycortone	Transdiaphragmatic	L.H.S. tot.	Hypotension, Hydrocortisone, Cortisone, DOCA		Hyperplasia degenerative phenomena
7	I	Hypophyseal X-ray		L.H.S. tot. Budapest			
	II	Hydrocortisone Spironolactone	Transdiaphragmatic	R.H.S. tot.	Pulm. embolism, temporary hypertension, Desoxycortone, Hydrocortisone	9.5	Z. fasciculata hyperplasia
8	I	Hypophyseal X-ray Spironolactone Potassium, Digitalis	Abdominal	L.H.S. tot.	Good general condition	10.6	Adenomatous hyperplasia
	II	Spironolactone Hydrocortisone Desoxycortone	Lumbar	R.H.S. tot.	Thrombosis, cardiac insuff., melaena, sepsis, Hydrocortisone, Cortisone	11.1	Z. fasciculata hyperplasia
9	I	Hypophyseal X-ray Spironolactone Potassium	Transdiaphragmatic	R.H.S. tot.	Hydrocortisone, Cortisone	9.2	Adenomatous hyperplasia
	II	Hydrocortisone Spironolactone Potassium	Transdiaphragmatic	L.H.S. tot.	Tension fluctuation, DOCA, Cortisone, Potassium	10.3	Diffuse hyperplasia
10	I	Hypophyseal X-ray Spironolactone Potassium Digitalis	Transdiaphragmatic	R.H.S. tot.	Normal conditions, Cortisone	12.7	Z. fasciculata adenomatous hyperplasia
	II	Hypophyseal X-ray Cortisone Desoxycortone	Transdiaphragmatic	L.H.S. tot.	Good general condition Cortisone, Hydrocortisone Desoxycortone	11.7	Z. fasciculata adenomatous hyperplasia

Table III (cont.)

No.	No. of operation	Preoperative treatment	Surgery	Adrenalectomy	Postoperative complication and treatment	Adrenal weight (g)	Histology
11	I	Hypophyseal X-ray	Transdiaphragmatic	L.H.S. tot.	Temporary icterus, Cortisone	7.8	Z. fasciculata moderate hyperplasia
	II	Digitalis Cortisone Desoxycortone	Transdiaphragmatic	R.H.S. tot.	Fever, anaemia, Digitalis, Hydrocortisone, Cortisone, DOCA	7.3	Z. fasciculata hyperplasia
12	I	—	Transdiaphragmatic	R.H.S. tot.	Normal conditions, Cortisone	7.9	Moderate hyperplasia
	II	Cortisone Desoxycortone	Transdiaphragmatic	L.H.S. tot.	Good general condition Cortisone, Desoxycortone	8.2	Z. fasciculata hyperplasia
13	I	—	Transdiaphragmatic	L.H.S. tot.	Cortisone	5.8	Z. fasciculata hyperplasia
	II	Cortisone Desoxycortone	Transdiaphragmatic	R.H.S. tot.	Good general condition, DOCA Hydrocortisone, Cortisone, Desoxycortone	6.8	Diffuse hyperplasia
14	I	—	Transdiaphragmatic	R.H.S. tot.	Good general condition, Cortisone	4.9	Moderate diffuse hyperplasia
	II	Cortisone Desoxycortone	Transdiaphragmatic	L.H.S. tot.	Temporary hypotension, Hydrocortisone, Cortisone, DOCA	5.7	Z. fasciculata hyperplasia
15	I	Hypophyseal X-ray Digitalis	Transdiaphragmatic	L.H.S. tot.	Good general condition, Hydrocortisone, Cortisone	7.1	Z. fasciculata nodular hyperplasia
	II	Cortisone Desoxycortone	Transdiaphragmatic	R.H.S. tot.	Cardiac insuff., Digitalis, Cortisone, DOCA	6.9	Z. fasciculata hyperplasia
16	I	—	Transdiaphragmatic	L.H.S. tot.	Good general condition	9.4	Z. fasciculata hyperplasia
	II	Cortisone Desoxycortone	Transdiaphragmatic	R.H.S. tot.	Fever, toxic dermatitis, hypotension, Hydrocortisone, Desoxycortone	9.8	Diffuse hyperplasia

Table IV

No.	Time since operation (years)	Substitution	Follow-up of patients
1.	8	Desoxycortone, then DOCA Cortisone	Temporary hypadrenia after operation II, later recurrence Operation III performed Body weight: 67 kg; blood pressure: 110/80 mm Hg. Does light work; frequent respiratory tract infections; adynamia; ulcer; hyperpigmentation; hypophyseal X-ray; normal menses
2.	12	?	Temporary hypadrenia; later normal conditions; substitution withdrawn. Body weight: 71 kg; blood pressure: 140/90 mm Hg. Not under observation
3.	14	Cortisone, desoxycortone	Hypadrenia; substitution necessary; is working. Body weight: 62 kg; blood pressure: 105/75 mm Hg
4.	13	—	Temporary hypadrenia; later normal conditions; normal menstruation; substitution not necessary. Body weight: 59 kg; blood pressure: 120/70 mm Hg
5.	9	—	Temporary hypadrenia; later recurrence; hypophyseal X-ray; hypertension; nephrotic syndrome; cardiac insufficiency. Body weight: 66 kg; blood pressure: 150/100—200/120 mm Hg. Death (1972)
6.	9	—	Recurrence after operation II; severe osteoporosis; cutaneous atrophy Operation III performed
	4 months	Cortisone DOCA	Satisfactory general condition. Body weight: 66 kg; blood pressure: 150/90 mm Hg
7.	6	Cortisone DOCA	Performs light work; duodenal ulcer; hyperlipaemia; norm. menses; norm. glucose tolerance. Body weight: 59 kg; blood pressure: 110/70 mm Hg
8.	6	Cortisone	Fit for work; ulcer disease; frequent infections; norm. glucose tolerance. Body weight: 63 kg; blood pressure: 140/80 mm Hg
9.	5	Cortisone, desoxycortone	Performs work; norm. delivery; hyperpigmentation; urinary tract infection. Body weight: 83 kg; blood pressure: 130/80 mm Hg
10.	4	Cortisone, desoxycortone, then DOCA	Performs light work; periodic retrosternal pains; norm. glucose tolerance. Body weight: 73 kg; blood pressure: 140/90 mm Hg
11.	2	Cortisone, DOCA	Performs light work; hyperpigmentation; frequent urinary tract infections; hypadrenic crisis; temporarily extrarenal azotaemia. Body weight: 72 kg; blood pressure: 120/70 mm Hg

Table IV (cont)

No.	Time since operation (years)	Substitution	Follow-up of patients
12	2	Cortisone, desoxycortone, then DOCA	Grown 16 cm; spontaneous menstruation; hyperpigmentation; attends school. Body weight: 38 kg; blood pressure: 110/65 mm Hg
13	2	Cortisone, desoxycortone, then DOCA	Grown 7 cm; moderately pigmented; is working. Body weight: 43 kg; blood pressure: 130/80 mm Hg
14	2	Cortisone, DOCA	Grown 14 cm; epiphyseal fugae open; irregular substitution; hypadrenic crisis; meningitis?; attends school. Body weight: 50 kg; blood pressure: 120/80 mm Hg
15	2	Prednisolone, desoxycortone	Performs light work; pregnancy; norm. glucose tolerance; osteoporosis decreased. Body weight: 96 kg; blood pressure: 140/90 mm Hg
16	1	Cortisone, DOCA	Performs work; hyperpigmented; no complaints. Body weight: 76 kg; blood pressure: 120/70 mm Hg

in patient 7, obviously as a consequence of the excessive steroid administration. Pneumo, thorax and pneumonia occurred in patient 5, a mild pulmonary embolization in patient 7 central circulatory failure in patient 15, fever and anaemia in patient 11, and fever and toxic dermatitis in patient 16. Most complications arose in patient 8: lower-limb phlebothrombosis, cardiac insufficiency, haemothorax, haematemesis, and then a reversible septic condition. In addition to electrolyte and fluid replacement and the use of antibiotics, 100 mg hydrocortisone and 10 mg water-soluble DOCA (Organon) were administered by drip infusion immediately after the operation; administration of 50 mg hydrocortisone was repeated at 6-hour intervals. Depending on the blood pressure and the general condition, the dose of hydrocortisone was gradually reduced, and replaced by cortisone acetate given by the intramuscular route. Continuation of mineralocorticoid therapy was necessary in most cases; 5 mg DOCA was given on the second postoperative day, and then desoxycortone every 2—3 days. In the first postoperative days preparations applicable in drip infusion were given preference as they allowed rapid adjustment of the dosage to the actual state, and eliminated the problem of drug absorption. The use of pressor substances was avoided as far as possible; only in patients 1 and 2 was a noradrenaline infusion employed for a brief period. Similarly, digitalis preparations were administered only exceptionally. Antibiotics were given in all cases to prevent infection.

The above scheme of treatment was never regarded as a rigid rule: the amount of hormone applied was always governed by the actual condition. When symptoms indicative of hypadrenia were observed, the dose of corticoids was increased. In contrast, if signs of overadministration appeared, the corticoid dose was reduced. The success of the operation depends primarily on adequate postoperative treatment. We ascribe it to the appropriate management that not a single patients was lost after adrenalectomy.

Histology of the adrenals

As seen in Table III the weight of most adrenals exceeded the normal average. Hyperplasia of the zona fasciculata and reticularis was generally present and was termed "diffuse hyperplasia". Hyperplasia of the zona reticularis dominated in patient 5, but in most cases the zona fasciculata was more hyperplastic. Microadenomas were found in five patients, and this was denoted as "adenomatous hyperplasia". In one case (patient 15) the adenomas had attained 4—5 mm in diameter ("nodular hyperplasia").

Data concerning substitution therapy and the fate of the patients are reported in Table IV.

Follow-up of the patients

Of the 16 patients, only one (case 2) is no longer under our observation, while patient 5 died from nephrotic syndrome nine years after the second operation. Patients 2, 4 and 5 had not been subjected to bilateral total adrenalectomy and so did not require long-term substitution. In one case (patient 3) continuous substitution therapy had to be prescribed in view of hypadrenia following bilateral subtotal adrenalectomy. For prolonged glycocorticoid treatment preference is given to cortisone acetate; a daily dose of 25—50 mg ensures a satisfactory general condition. In addition, mineralocorticoids are given: 5 mg of desoxycortone every 7—14 days. Recently sublingual DOCA (Organon) has been successfully used in several patients; their blood pressure and electrolyte balance could be maintained at suitable levels with a daily dose of 2—4 mg. Naturally, in the event of any serious intercurrent disease considerably higher doses are required.

In patient 5 the left subtotal and right total adrenalectomy was followed by temporary hypadrenia, but later the hypercorticism recurred. The patient refused the third operation. Meanwhile hypertension and a nephrotic syndrome developed, and the patient died 9 years after the second operation. In two other cases (patients 1 and 6) there was a recurrence after total adrenalectomy on one side and subtotal adrenalectomy on the other, and thus a third operation became necessary; removal of the hypertrophied adrenal stump was followed by the disappearance of hypercorticism. Of the six patients with subtotal adrenalectomy, only in two (patients 2 and 4) did adrenocortical *function return to normal.* In patient 3, in spite of the fact that only subtotal adrenalectomy had been carried out on both sides, lasting hypadrenia developed and continuous substitution therapy was necessary.

For the reasons explained above, the later course of patients 2, 4, and 5 is not analyzed below. Of the remaining 13 patients, 12 are able to perform light work or to attend school. A hypadrenic crisis occurred in two patients on one occasion; it was ascribed to irregular substitution. In both cases appropriate drug administration was followed by rapid restoration of the condition.

Body weight fell appreciably in two thirds of the cases. In the first two years after the operation the height of the three patients with juvenile-type Cushing's disease increased by 16, 7 and 14 cm, respectively; before operation, their height had been constant for a number of years. Blood pressure had been high in 9 of these 13 patients; following bilateral adrenalectomy the hypertension ceased in all of them. Hyperpigmentation was observed in half of the patients. Systematic lateral cranial X-ray examinations have not revealed sellar enlargement in any of the patients, but this does not yet exclude the possible presence of adenomata. Frequent infections of the urinary and respiratory tract were observed in four patients, and ulcer disease in

three. With one exception, the decreased glucose tolerance became normal. Menstruation was normalized in five patients; of these, patient 9 delivered a full-term child after an uneventful pregnancy, while patient 15 was subjected to an artificial abortion. The growth of hair decreased markedly in every female patient suffering from hirsutism. The previously observed active striae disappeared in every case; nor could signs of cardiac insufficiency be detected. Osteoporosis improved considerably in one subject (patient 15).

To sum up, the patients' symptoms either disappeared completely, or improved considerably. Within 2—3 months after the second adrenalectomy the condition of the patients had stabilized, and disregarding minor sensation of weakness they felt satisfactorily well under the substitution therapy.

Own experience

a) *Surgical indication*

In the case of adrenocortical hyperplasia the indication for surgery is often difficult. The clinical signs of adrenocortical hyperfunction are often mild, and the laboratory differences frequently insignificant. In such cases we restrict the calorie intake and carry out X-ray irradiation of the hypophyseal region. Drug therapy should be attempted in the first place as in mild cases spontaneous remission sometimes occurs [36, 58]. If the condition of the patient does not improve on conservative treatment, the process progresses rapidly, and the danger of irreversible damage (diabetes mellitus, severe osteoporosis, etc.) is imminent, adrenalectomy becomes necessary. Of course, if the symptoms are pronounced, if the laboratory data are indicative of a considerable adrenocortical hyperfunction, and if a rapid progression of the disease can be reckoned with, then there is no reason to wait as heart failure soon appears in Cushing's disease and greatly augments the risk of surgery.

Adrenalectomy is contraindicated if the surgical risk is too high in comparison with the expected result. Although the safety of the operation has increased in recent years and suitable hormone preparations have become available to combat postoperative hypadrenia, it must be borne in mind that removal of the adrenals is still associated with considerable risk. In a given case the success of surgery may be adversely affected by latent cardiac insufficiency, disturbed electrolyte balance, kidney disease, and obesity. In such cases the most important task is to prescribe adequate drug treatment in order to render the patient suitable for operation as soon as possible. In our experience, in well-prepared patients the operative risk is slight.

b) *Surgical considerations*

Three questions arise as regards the surgical problems: should the adrenalectomy be unilateral or bilateral, should it be total or subtotal, and should the operation be carried out in one or two stages?

Experience shows that the hyperplasia is usually bilateral, and so the problem is not solved by removal of one of the adrenals. After unilateral adrenalectomy, ACTH mobilization is significantly enhanced and this may mean a further stimulation of the remaining adrenal cortex.

The other problem is whether the adrenalectomy should be total or subtotal. There is no doubt that subtotal adrenalectomy would be the ideal solution, for it provides the possibility to eliminate hypercorticism, and to render the patient eucorticoid. Unfortunately, these hopes attached to subtotal adrenalectomy are rarely realized in practice. We have carried out subtotal adrenalectomy in 6 cases, and only in 2 (patients 2 and 4) was a eucorticoid state be achieved, in spite of the fact that the adrenal substance left over was in fact minimal, and even its blood supply was questionable. In such cases the remaining adrenocortical tissue seems to regenerate as a result of ACTH hypersecretion, and gradually becomes hypertrophied. Hence, the temporary relief may be followed by hypercorticism. Recurrence was observed in 3 of our subtotally adrenalectomized cases (patients 1, 5 and 6), and a third operation was performed on patients 1 and 6. To find and to remove the residual adrenal stump is not easy. On the other hand, even subtotal adrenalectomy may be followed by hypadrenia (patient 3). This may be due either to the fact that too little functioning adrenocortical tissue was left over or that the adrenal residue became necrotic because of the loss of adequate blood supply.

An unanimous standpoint has not developed with regard to the technique of the operation [18, 39, 54]. Ellison [6] regards the abdominal approach as the most appropriate. We have employed upper laparotomy only exceptionally, as the obesity common to most patients may interfere with good exposure. Still, in selected cases (good general condition, and a not very fat patient) bilateral adrenalectomy through an abdominal incision is justified.

The thoracic approach which we now apply is surgically more simple, provides an easy access to the adrenal, and causes less postoperative discomfort to the patient. Its obvious disadvantage compared to the abdominal approach is that it permits the removal of only one adrenal gland at a time.

A number of authors suggested bilateral adrenalectomy in one stage [7, 22]. We feel that the simultaneous removal of both adrenals may represent an unjustifiable load. Bilateral thoracotomy in one stage would considerably interfere with satisfactory pulmonary ventilation and cannot therefore be recommended. Accordingly, we carry out our operations in two stages. The interval between the two interventions has varied from a few weeks to 2 years.

c) *Dangers of the operation*

Bilateral total adrenalectomy is obviously followed by definite hypadrenia necessitating life-long corticoid substitution. With appropriate treatment,

prognosis is favourable so far as survival is concerned but with any intercurrent stress (operation, infections, etc.) the corticoid requirement is augmented and thus the usual hormone dose must be increased.

After removal of the adrenals hyperpigmentation frequently appears on the skin and the mucous membranes. This is an unpleasant complication from the cosmetic aspect, but naturally does not endanger the life of the patient.

In recent years it has been observed that ACTH-producing adenohypophyseal tumours and chromophobic adenomas may develop in adrenalectomized patients [1, 30, 32, 33, 44, 47]. In large series enlargement of the sella turcica occurred with a frequency of 5.0—16.0% [13, 17, 53, 56]. Hypophyseal tumours subsequent to adrenalectomy are not infrequently malignant [42, 48, 56]. Growth of the sella turcica did not occur in our material, probably due to X-ray irradiation of the hypophyseal region. It is improbable that the substitution employed would play an important role in the absence of hypophyseal tumours, for it is known that the enhanced ACTH production of individuals adrenalectomized because of Cushing's disease can be suppressed only with a large dose of corticoids [23, 25]. Still, in our cases the observation period might have been too short for the development of a hypophyseal tumour.

d) *Pre- and postoperative treatment*

As regards the success of the operation, medical management is of fundamental importance. In addition to the preoperative investigations necessary for correct diagnosis and for excluding presence of a tumour, it may be necessary to treat the patient's heart. In the event of hypokaliaemia and sodium retention, potassium administration and sodium withdrawal are recommended. Application of spironolactone (Aldactone) has a good effect in such cases.

One of the important questions is whether corticoids should be given preoperatively. In our opinion this is only justified if hypadrenia is to be expected during the operation. Preoperative corticoid administration is recommended before the second stage operation, and also if there is a probability of an adrenocortical tumour. The reason is that in this case the contralateral adrenal cortex will probably undergo atrophy. It is recommended to administer 50—100 mg cortisone intramuscularly on the evening before the operation. This dose is repeated in the morning before the operation, when 5 mg of desoxycortone are given in addition. After this pretreatment no hydrocortisone drip infusion was needed during the operation.

In the immediate postoperative period, careful observation of the patient is extremely important. It is not possible to lay down exact rules as regards treatment. It must, however, be stressed that the success depends primarily on adequate postoperative treatment. The decision as to what should be given, and how much, is governed by the patient's actual condition. In general we

administered 50 mg hydrocortisone every 6 hours after the operation, with 5 mg DOCA at 12-hour intervals, by intravenous drip. Depending on the patient's condition, this dose is gradually reduced on the next two days, and after the fourth postoperative day the hydrocortisone is replaced by cortisone acetate, and DOCA by long-acting desoxycortone. If the blood pressure decreases, the dose of corticoids is increased, and (rarely) even noradrenaline may become necessary. Administration of pressor drugs should be restricted to the minimum, as the glycocorticoids are known to potentiate the vasoconstrictive effect of noradrenaline [24, 40, 45, 50], with a resulting impairment of the blood supply to important organs.

Oral corticoid therapy is started after about one week. The doses providing permanent substitution are introduced two weeks after the operation. The general state of our patients was more favourable if cortisone acetate was administered; 1—3 doses were required daily. In addition, mineralocorticoid must be given in most cases: the dose of desoxycortone is 5 mg every 1—2 weeks, although more recently we favour the use of sublingual DOCA tablet (2—4 mg daily).

e) *Perspectives*

The question was long ago raised as to whether it would be better to perform hypophysectomy instead of adrenalectomy, as the disease is in essence of hypothalamo-hypophyseal origin. There is no doubt that the hypercorticism caused by adrenocortical hyperplasia may be eliminated also by removal of the hypophysis; nevertheless, we prefer adrenalectomy. The reason is not only that adrenalectomy is a less severe surgical intervention and is associated with less surgical risk, but primarily that hypophysectomy, apart from the hypocorticism, may induce irreversible hypothyroidism and hypogonadism, together with disturbances of water metabolism. To perform hypophysectomy instead of adrenalectomy is justified only if the hypercorticism is brought about by a large hypophyseal tumour causing increased intracranial pressure and threatening the optic nerve [5, 28, 31, 41]. Good results have recently been attained by the implantation of radioactive gold or yttrium into the sella turcica [2].

Concerning the therapeutic principles future possibilities should also be considered. Although the views expressed in this paper may appear up-to-date and correct at the moment, we nevertheless feel that considerable changes are to be expected in the future with regard to the indication of adrenalectomy. There is no doubt that "chemical adrenalectomy" instead of the surgical removal of the glands would be the ideal solution, if the patient could be made eucorticoid by the administration of drugs inhibiting the pathologically enhanced production of hormones, and if the irreversible hypadrenia could be avoided. Research into inhibitors of hormone production has been going

on for a number of years, and further progress is to be expected. As regards the adrenal cortex we are already fairly familiar with the steps of hormone production and with the enzymatic mechanisms involved in the transformation of the precursors. It may well be that the time is not too far when suitable inhibitors will be found. The initial results are encouraging. Aminoglutethimide has been used effectively in the treatment of Cushing's disease [10, 27]. In addition, several inhibitors of corticoid synthesis have already been produced, and their use has been tested in cases of hypercorticism, and particularly of adrenocortical carcinoma producing corticoids [4, 15, 19, 20, 21]. Unfortunately, their administration is at present limited by their toxicity. The production of further, effective but harmless drugs is a fundamental task for the future.

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