



# Treatment of Pituitary Adenomas

First European Workshop on Treatment of Pituitary Adenomas at Rottach-Egern

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With a Foreword by Frank Marguth

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## Diagnosis and Treatment of ACTH-Producing Pituitary Tumors

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### Introduction

In contrast to the almost clear-cut concept in treating growth hormone and prolactin producing pituitary tumors it seems to us more difficult to manage ACTH-producing pituitary tumors. One reason is certainly our rather limited experience due to the lack of cases with these ACTH-producing adenomas which are the least frequent endocrine active adenomas if one does not take into consideration rareties such as glycoprotein-producing pituitary tumors. The other reason is most likely the resistance of the corticotrophic cell which is well established from the pathophysiology of pituitary diseases. The following study deals with our experience in treating patients with ACTH-producing adenomas whom we have divided into two groups: Firstly patients with Cushing's disease with a pituitary tumor and secondly patients with Nelson's syndrome.

### Patients and Methods

We studied 22 patients altogether, 7 with Cushing's disease and pituitary adenoma and 15 with Nelson's syndrome. Details of the findings in our patients are summarized in Tables 1 and 2. Cortisol and thyroxin levels were measured by radioimmunoassay (RIA) or competitive protein-binding assay [1]. The ACTH levels were measured by RIA or by bioassay (in vitro corticosterone production by isolated adrenal cells according to Sayers et al. [2, 3]) both after ACTH extraction from plasma on silica-gel columns (unpublished). Synthetic human ACTH served as ACTH standard, kindly supplied by CIBA-GEIGY AG, Basel, Switzerland (1-39-h-ACTH, CGP 2917). The preliminary

normal range for the plasma, ACTH level at 9 a.m. with these methods is between 20 and 100pg/ml. TSH, hGH, hPRL and LH levels were measured by RIA with double-antibody methods [4].

**Results**

**Patients with Cushing's Disease and a Pituitary Tumor (n=7)**

The preoperative and postoperative findings are summarized in Table 1. Only 2 patients had considerable enlargement of the sella turcica whereas in the other 5 only a minor enlargement could be demonstrated by standard lateral skull x-ray or tomography. Only in 1 of the patients (S.W.) was there suprasellar extension of the pituitary tumor as demonstrated by visual field defects. Hypercortisolism was documented by elevated

**Table 1 Endocrine Evaluation, Operative Procedure and Tumor Histology in 7 Patients with Cushing's Disease and Pituitary Tumor**

- n = normal
- ↑ = elevated
- ↓ = diminished
- = no change (preoperative)  
or not present (postoperative)
- IHT = insulin-hypoglycemia-test
- ts = transphenoidal
- tf = transfrontal
- cryo = cryohypophysectomy
- rad = radiation

*Preoperative*

	Sex	Age years	Serum Cortisol level				IHT		Lysine-Vasopressin	LIDDLE-test	ACTH	Sella	Serum thyroxine	TRH test		LH-RH test LH
			basal	after 25 IU ACTH	after 2mg dexamethasone	diurnal rhythm	Cortisol	hGH						TSH	hPRL	
E.R.	♂	31	↑	↑	↑	—	—	—	↑↑		(↑)	n	(↓)			
H.M.	♀	63	↑	n	(↑)	—	—	(↑)		↓	(↑)	n	(↓)	n	n	
M.Ch.	♀	33	↑	n	↑	—	—	—		↓	↑	(↑)	n	n	n	
M.R.	♂	33	↑	↑	↑	—	—	—	↑↑		(↑)	n	n	n	n	
H.J.	♀	34	↑	↑	↑	—	—	—		↓	↑	(↑)	n	n	n	
F.F.	♂	45	↑	n	↑	—				↑↑	↑	n	(↓)		↓	
S.W.	♂	50	↑	↑	↑	—				↓		↑↑	↓	↓	n	↓



## Postoperative

	Sex	Age (years)	Operation	Histology	Clinical signs of hypercorticism	Hypothalamo-pituitary-adrenal axis	hGH	TRH test		LH-RH test	Diabetes insipidus
								Serum thyroxine	LH		
							TSH	hPRL			
E. R.	♂	31	ts	adenoma	—	n	n	n	n	n	—
H. M.	♀	63	ts	adenoma	—	n	n	n	n	n	—
M. Ch.	♀	33	ts	adenoma	—	(↑)	(↓)	n	n	n	—
M. R.	♂	33	ts	adenoma	+	↑	↓	n	n	n	—
H. J.	♀	34	ts	adenoma?	+	↑	(↓)	n	n	n	—
F. F.	♂	45	ts + Cryo	adenoma	—	↓	↓	↓	↓	↓	+
S. W.	♂	50	ts + Cryo	ad. with signs of enhanced prolif.	—	↓	↓	↓	↓	↓	+
		preop. 2			+	↑	↓	↓	↓	↓	—
		postop. 2	tf + rad.	ad. with signs of enhanced prolif.	↓	(↓)					+

basal serum cortisol levels, hyperresponsiveness to exogenous ACTH, failure of suppression or subnormal suppression by dexamethasone and abolition of the circadian rhythm. Typically for this disease, none of the patients showed a rise of cortisol levels after adequate hypoglycemia and growth hormone secretion was blunted. ACTH dependency of cortisol secretion was documented by either an exaggerated rise of serum cortisol levels after lysine-vasopressin or suppression of the urinary corticosteroid excretion after large doses of dexamethasone or elevated ACTH levels. The other pituitary functions were not disturbed except in the two patients with the larger adenomas.

In the 5 patients with only slight sellar enlargement a selective transsphenoidal adenectomy was performed. In the first two cases (E. R., H. M., Table 1) not only the clinical picture of Cushing's disease disappeared completely, but there was also total normalization of the anterior pituitary function including the hypothalamo-pituitary-adrenal axis [5]. This was demonstrated by the postoperative cortisol stimulation and suppression data in these patients: the basal serum cortisol level was within the normal range and showed normal suppression after 2 mg dexamethasone overnight and stimulation by intravenous ACTH. The endogenous ACTH level showed normal stimulation by insulin-induced hypoglycemia as reflected by a normal rise of the serum cortisol level. The insulin dose necessary to achieve adequate hypoglycemia was half or less of the preoperative dose corresponding well to the disappearance of the diabetic carbohydrate metabolism in these patients. One patient (E. R.) showed a normal diurnal variation.

Sex	Age (years)	Time of adrenalectomy	Sella at the time of adrenalect.	First signs of sella enlargement	hGH	Serum thyroxine	TRH test		LHRH test LH	ACTH (ng/ml)	Increase of sella size	Other indications for hypex.
							TSH	PRL				
M.K.	38	7/1961	n	1967	n	n	n		sex horm.	0.9	-	-
M.T.	37	1/1972	n	11/1972	n	n	n	n	n	0.27	-	-
L.E.	29	8/1962	n	3/1966	n	n	n	n	n	1.1	-	-
K.Sch.	40	4/1960	n	10/1974	n	n	n	n	n	>10.25	-	-
R.B.	34	9/1970	n	10/1975	n	thyroid hormones	↓	n	n	0.92	-	-
H.H.	62	11/1957	n	5/1973	n	n	n	n	n	1.74	-	-
R.E.	31	2/1966	n	1968	n	n	n	n	sex horm.	15.01	+	
A.L.	41	5/1964	n	1968	↓	n	(↑)		↑	2.22	+	amenorrhea
J.K.	40	11/1966	n	1969	n	n			n	0.31 <sup>+</sup>	+	infraselar sphenoidal extension
A.La.	29	1/1971	n	1972	n	n	n	n	n	12.39	-	amenorrhea, pregnancy desired
M.M.	49	8/1960	n	1968		n	↑	n	n	1.74	+	
G.Sen.	30	12/1966	n	1969	n	n	n	n	n	2.87	+	
E.B.	39	11/1969	?	90 <sup>1971</sup> (q-impl.)	↓	thyroid hormones	↓		↓	0.59 <sup>+</sup>	(+)	ophthalmoplegia
R.H.	48	11/1971	+	1971					↓	0.60	++	ophthalmoplegia
S.M.	15	1/1972	n	11/1972	(↑)	n	n	n	n	0.12 <sup>+</sup>	++	bitemporal hemianopsia

Table 2 Summary of the Preoperative Data of 15 Patients with Nelson's Syndrome. (for explanations of symbols see Table 1; ACTH levels marked with an asterisk are measured in unextracted plasma)

Although the other (H.M.) had an abnormal circadian rhythm, the disappearance of abnormal cortisol secretion in this patient was documented by low normal urinary excretion of cortisol metabolites and free cortisol. The male patient who had preoperatively shown and exaggerated serum cortisol response after lysine-vasopressin now had a normal rise of serum cortisol during this test. In the next two patients (M.Ch., M.R.) a microadenoma was found during operation and confirmed by microscopic examination. In both cases hypercortisolism persisted postoperatively, whereas again the other pituitary functions remained intact. Despite these conflicting findings and with renewed postoperative increase of her ACTH level (Fig. 1) the female patient

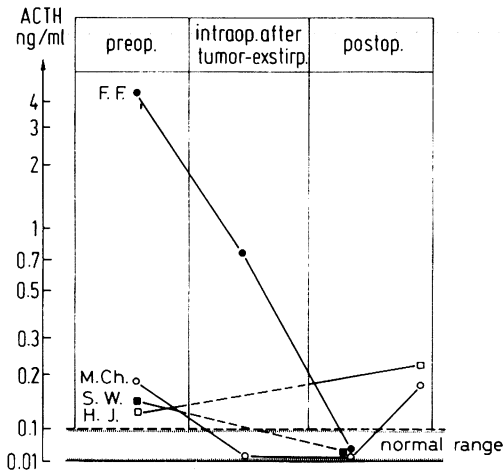


Fig. 1 Summary of the pre-, intra- and postoperative ACTH levels in four of the patients with Cushing's disease (Table 1)

showed complete clinical remission of Cushing's disease with normalized menstrual bleedings. In the female patient H.J. the neurosurgeon already could not make out the adenoma with absolute certainty, nor could this diagnosis be confirmed by histological examination. In keeping with these negative findings the clinical picture of the not very active Cushing's disease persisted, in agreement with still elevated cortisol and ACTH levels (Fig. 1).

In two patients with the larger tumors (F.F., S.W.) cryohypophysectomy was performed in addition to a transsphenoidal operation. One of these patients (F.F.) had shown extremely elevated ACTH levels comparable to those found in Nelson's syndrome (Fig. 1). In both patients the clinical and laboratory findings of Cushing's disease were abolished and panhypopituitarism including diabetes insipidus were encountered. In one case (S.W.), in whom the microscopic examination had revealed signs of enhanced proliferation, Cushing's disease recurred one and a half years after the first operation accompanied by an invasively growing tumor. A second operation had to be performed on this patient by the transfrontal approach, followed by radiation therapy which has only just been completed (Table 1). For the time being the signs of Cushing's disease have regressed and a low normal basal cortisol and ACTH level has been observed (Fig. 1). The prognosis in this patient is uncertain.

Our results have led us to believe that there are two different mechanisms leading to Cushing's disease. Some patients have a circumscribed autonomous pituitary adenoma [6, 7] which can be selectively removed; this was demonstrated in two of our patients [5], one of whom has been in remission for more than five years after operation. The other mechanism seems to consist of a hypothalamic stimulus leading to pituitary corticotrophic hyperplasia with or without adenoma formation [8, 9]. For the latter type, our cases showing no remission postoperatively despite histologically proven adenectomy may provide good evidence.

## Patients with Nelson's Syndrome (n=15)

In patients with Nelson's syndrome [10,11] the interpretations of clinical and laboratory findings are even more conflicting [12]. Our definition of this syndrome includes hyperpigmentation, markedly elevated ACTH levels and — most important — evidence of a pituitary tumor, as demonstrated by skull x-ray.

Table 2 summarizes the preoperative clinical and laboratory data in 15 patients with Nelson's syndrome. They are subdivided into two groups: the first consists of patients not operated upon, the second contains the patients who received surgical treatment. In the patients of the first group there was a long period of latency between adrenalectomy and sellar enlargement with the exception of one patient (M.T.). In all of them the pituitary tumor was small and there was no evidence of anterior pituitary dysfunction and no progression of tumor growth for up to ten years. In the second group (n=9) the period between adrenalectomy and tumor development was in general shorter, in one patient (R.H.) a pituitary tumor was suspected already at the time of adrenalectomy. The sella size increased during the follow-up period and in four cases (J.K., E.B., R.W., S.M.) the tumor grew out of the fossa turcica. In these 9 patients there was also evidence of anterior pituitary insufficiency, particularly in the patients with suprasellar extension of the tumor. The ACTH levels were always elevated and showed considerable variation without differing significantly in the two groups. This is also true for the ACTH levels after administration of dexamethasone, which are in general lower than the basal ACTH levels, and for the ACTH secretion stimulated by insulin-induced hypoglycemia (Fig. 2). Therefore no therapeutical consequences can be derived from the ACTH measurements alone.

Table 3 summarizes operative procedures, tumor histology and postoperative endocrine evaluation of the nine patients operated upon. Four patients were operated upon by the transphenoidal approach; the ACTH levels fell only slightly postoperatively. One patient (R.E.) was operated upon a second time after which an initial fall of the ACTH level was observed, which, however, increased again during later follow-up investigations. One patient (A.La.) became pregnant postoperatively. One of these

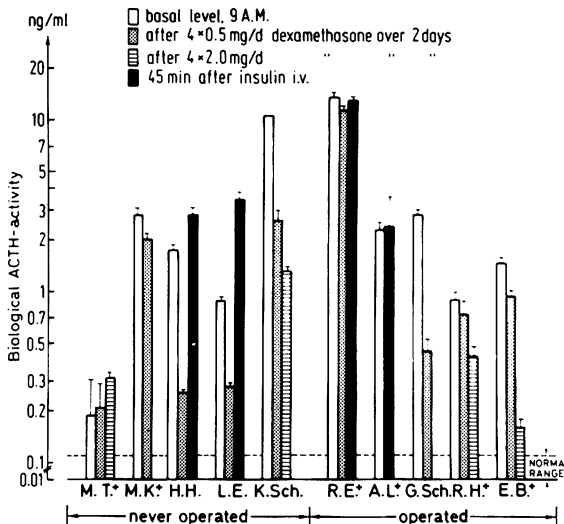


Fig. 2 ACTH levels after various doses of dexamethasone and after insulin-hypoglycemia in patients with Nelson's syndrome (mean  $\pm$  SD). In patients marked with asterisk bioassay was performed according to Lipscomb and Nelson [13, 14]

sex	Age (years)	Operation	histology	ACTH (ng/ml)	anterior pituitary function	Diabetes insipidus	Postoperative follow up	Sella size
♀	31	ts 8/71 ts 8/72	adenoma adenoma	14.78 3.51 ↓	n n	- -	ACTH ↑↑ (26.9)	- C
♀	41	ts 8/71	adenoma	1.98 (↓)	n	-	ACTH ↑↑ (109.05)	C
♂	40	ts 7/71	adenoma	0.29 (↓)	↓	-		C
♀	29	ts 4/72	adenoma	12.4	n	-	2 x pregnancy ACTH: ↓ (4.2)	C
♀	49	ts 9/74 + cryo	adenoma	0.04 ↓	↓	+		C
♀	30	ts 7/74 + cryo	adenoma	0.03 ↓	↓	+		C
♀	39	tf 1/74 + rad.	adenoma	1.12	↓	-	regression of ophthalmoplegia	C
♂	48	ts 5/72 + cryo tf 2/73 + rad. tf 12/74	adenoma adenoma adenoma	0.63 0.68 ↓ 1.75	↓ ↓ ↓	- - +	ACTH ↓ (1.78) amblyopia left hemianopsia right ± 7/75	↑ ↑ -
♀	15	ts 8/74 + cryo tf 2/75 + rad.	adenoma with signs of enhanced proliferation undifferent. adenoma	<0.1 ↓ <0.01 ↓	↓ ↓	- +	ACTH ↑ (1.65)	↑ C

Table 3 Summary of Postoperative Data in 9 Patients with Nelson's Syndrome (for explanation of symbols see Table 1; c = constant)

patients (A.L.) documents the discrepancy between clinical improvement and ACTH level quite clearly (Fig. 3). Whereas after operation the cyclic ovarian function became normalized, the sella size remained unchanged and pituitary function returned to normal, there was constant increase of the basal ACTH level.

Two patients (M.M., G.Sch., Table 3) were operated upon by the transsphenoidal route with additional cryohypophysectomy; postoperatively panhypopituitarism and diabetes insipidus were observed. Both patients showed depigmentation and their ACTH level decreased to low-normal values. The three patients with large tumors and ophthalmo-

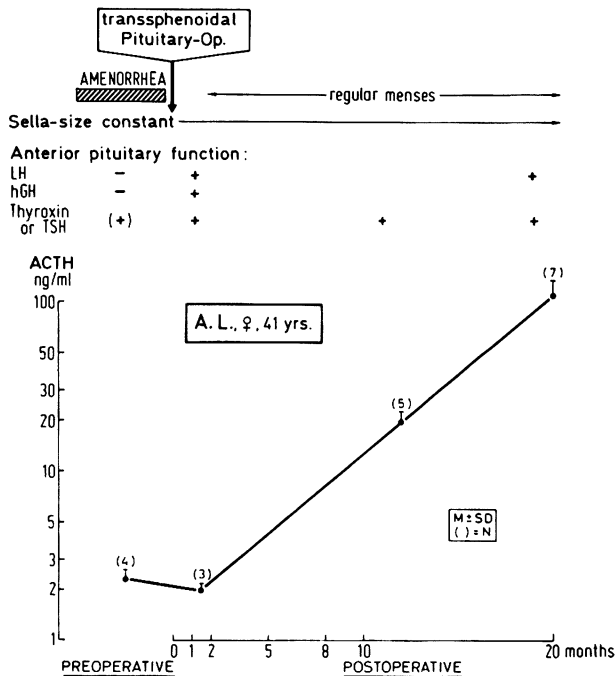


Fig. 3 ACTH levels and anterior pituitary function pre- and postoperatively in a woman with Nelson's syndrome

logical symptoms were operated upon by the transsphenoidal or transfrontal route in combination with radiotherapy and/or cryohypophysectomy. The second operations were necessitated by progressing tumor growth, increasing ACTH levels and deterioration of vision. Complete panhypopituitarism had to be encountered. Two patients are now on remission whereas one patient died half a year after the third operation due to invasive growth of his pituitary tumor.

### Conclusions

The data we have accumulated suggest that patients with Cushing's disease and pituitary tumors and patients with Nelson's syndrome have the same underlying disease appearing in various modifications. They have the following in common:

1. Occurrence of
  - either small adenomas with a minimal growth potential
  - or large, potentially invasive tumors.
2. Extremely high ACTH levels, occasionally occurring also in Cushing's disease.
3. Histological and electronmicroscopic appearance of the adenomas [5, 15].
4. Probably either autonomous adenoma of the pituitary or hypothalamic CRF-excess as primary cause.

However, Cushing's disease with pituitary adenoma and Nelson's syndrome differ in respect of therapy requirements. In the patients with Cushing's disease neurosurgical treatment should cure the hypercortisolism and the tumor, whereas in cases with Nelson's syndrome the indication for surgical treatment depends upon tumor size and the rapidity of growth.

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