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SUCCESSFUL METYRAPON (M) TREATMENT FOR CUSHING'S DISEASE
(C D) IN AN ADOLESCENT BOY.

A 14 year old boy presented with growth retardation and delayed gonadarche in presence of adrenarche, discrete obesity of trunk and face, delayed bone age, osteoporosis and biochemical hypercortisolism: plasma cortisol (F) 24h-profile was elevated but hypopulsatile (mean 22.1 ng/ml \pm 13%) and without diurnal variation; urinary free F and 20 α -dihydro-F were increased (86.4 and 370.0/24h). C T-scans of pituitary and adrenals were unremarkable. Normal ACTH-levels (8 a.m.: 31.3 pg/ml) and maintenance of a circadian rhythm were not entirely consistent with C D, but good F-suppression by 0.5 mg Dexamethasone or 1500 mg M and adrenal stimulation by ACTH and CRF -via ACTH- indicated a central origin of hypercortisolism. 24h-secretion of gonadotropins was suppressed and hypopulsatile; HGH was reduced during sleep and after GHRH-stimulation. After a 4-month-therapy with 2 x 250 mg M, the following changes were measured: decrease of mean 24h plasma F (3.7 ng/ml \pm 37%) and DHEAS (4406 vs 3333 ng/ml); slight elevation of ACTH (40.1 pg/ml) and increase of testosterone (0.59 vs 4.9 ng/ml, LH (1.8 vs 7.1 ng/ml), FSH (3.9 vs 6.7 ng/ml) and HGH (max. nocturnal peak: 10.5 vs 18 ng/ml). Normal renin activity and high somatomedin C were unchanged. Clinically the patient exhibited catch-up growth and an increase of testicular volume without adverse M-effects.

Conclusion: If surgery is not feasible, M may be an effective long-term medication for hypercortisolism in adolescents.

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144 SUPPRESSION OF THE PULSATILE SECRETION PATTERN OF LH
AND HGH IN AN ADOLESCENT BOY WITH CUSHING'S DISEASE.

Cushing's syndrome is frequently associated with growth retardation and decreased gonadal function. So far, the underlying mechanisms of these disturbances are poorly understood. An 18 year old boy is described who was referred because of delayed puberty (bone age 12 years) and short stature (145.5 cm). The patient had a typical cushingoid habitus. His testes were preadolescent in size (4-5 ml), and the testosterone was low (18 ng/dl). 24h plasma cortisol levels were consistently high (32.3 \pm 5 μ g/dl) with episodic increases. ACTH was elevated (126 \pm 44.6 pg/ml), and the cortisol spikes could be related to concomitant ACTH bursts. 24h profiles of LH and HGH exhibited low levels (LH, 2.52 \pm 0.51 mU/ml; HGH, 0.58 \pm 0.5 ng/ml), and the pulsatile secretion was completely abolished. HGH failed to respond to arginine infusion, insulin-induced hypoglycemia, and GRF1-44. LHRH-stimulation produced a prepubertal increase of LH: 0 min, 2.95 mU/ml; 30 min, 8.2 mU/ml. Surgery revealed an ACTH-producing microadenoma of the pituitary. 3 months after complete extirpation of the tumor LH and HGH showed normal pulsatile secretion patterns (9 pulses per 24 h), and testosterone had begun to normalize (414 ng/dl). After 1 year of observation, testicular size was 12-15 ml, and growth velocity was 10.6 cm/year. It is suggested that the delay of puberty and growth was due to the suppression of the pulsatile secretion of LH and HGH, caused by the hypercortisolism.

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145 CUSHING'S SYNDROME, IDENTIFICATION OF ACTH SOURCE BY
SELECTIVE CATHETERIZATION AND ACTH AND β -LPH ASSAYS

The differential diagnosis of ACTH dependent Cushing's syndrome (85% of patients) can be very difficult. Localization of an ACTH source is not always possible with CAT-scan and MRI imaging. A bilateral catheterization of the inferior petrosal sinus with blood sampling for ACTH/LPH during a CRH test has been used for localizing a pituitary adenoma. ACTH was measured with a solid-phase antiserum against the 11-24 sequence of ACTH (sensitivity 16-32 pg/ml). For β -LPH, the reagents of NIAMDD have been used. Samples were obtained before and at 5-min. intervals for up to 30 min. after injection of CRH, 100 μ g/1.73 m². In 18 of 21 patients, a pituitary ACTH source could be proven and in 16 an adenoma localized. In 12 of 18, peripheral ACTH levels were <100 pg/ml (6 <40 pg/ml). Mean basal/peak ACTH (LPH) pg/ml: Periphery 87/256 (551/845), tumourside 899/1870 (3424/11572), contralateral 427/647 (1467/2034). In 6 of 18 patients, only CRH stimulated levels pointed to the correct side. The mean Δ ACTH (LPH) (ipsilateral to contralateral) increased from 172 (1957) before to 1223 (9529) after CRH. In conclusion, selective catheterization and ACTH/LPH assay after CRH is valuable for detecting the ACTH source and thus allows a selective surgery, preserving the pituitary tissue, which is of utmost importance, especially in the pediatric age group.

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URINARY STEROID PROFILE IN CHILDHOOD CUSHING'S
DISEASE.

Numerous urinary steroids were measured before treatment in 9 children (8F, 1M) with Cushing's disease: 4 patients with pituitary dependent adrenal hyperplasia (H), 1 with bilateral micronodular dysplasia (MD), 2 with adrenal adenoma (A) and 2 with adrenal carcinoma (C). Important steroids or steroid-group-excretions are shown in mg/24 h compared to normals (N):

	AGE	Σ THF	THS	Σ THB	P-triol	Δ -5-P-triol	17KS	16-OH-DHA
H	5	16.9	0.6	1.6	0.6	<0.1	0.7	<0.1
	8	14.4	0.5	0.6	1.0	0.1	0.1	<0.1
	10	10.3	0.4	1.6	0.5	<0.1	1.1	<0.1
	12	9.7	0.4	0.9	0.9	<0.1	1.6	<0.1
MD	4	6.2	0.8	1.7	<0.1	<0.1	0.9	<0.1
A	4	9.0	0	1.3	0.3	0	0.5	<0.1
	10	8.9	0.7	<0.2	0.3	<0.2	0.4	<0.1
C	2	18.2	2.2	4.0	1.6	15.6	138.2	7.6
	14	51.4	5.2	1.4	6.1	1.2	19.2	11.3
N	<14	<3.6	<0.3	<1.2	<0.5	<0.2	<2.0	<0.1

The excretion of total cortisol metabolites (Σ THF) was increasing in the order of MD < A < H < C, THS in order of H < A < MD < C. P-triol, Δ -5-P-triol, 17KS and 16-OH-DHA were highly increased in the carcinoma patients. Distinction between malignant and benign tumor was therefore possible, whereas no distinction between adenoma and micronodular dysplasia was seen.

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CORTISOL ASSESSMENT OF BABIES BORN FROM
MOTHERS TREATED BY GLUCOCORTICOIDS

Basal and stimulated (IM .125 μ g of short-acting Synacthen) Cortisol (F) levels were evaluated in 34 babies (Treated) born from mothers treated with Glucocorticoid [Prednisone (5-100) or Bethametasone (.5-3.5) mg/day] either over the whole pregnancy or the last 1-22 weeks. Results were compared with age-matched Control groups (Wilcoxon test). In spite of the 50% Basal F values lower than 60 ng/ml observed in the 0-90 (n=80) day (d.) old Controls, results from Treated were lower (p<.01). The 5 Treated tested after 3 months (m.) did not exhibit the significant increase of Basal F to 93 \pm 7 ng/ml (mean \pm SEM) normally observed. Stimulated F from Controls reached identical values whatever the age group considered [0-6 d., 208 \pm 8 (n=4); 7-90 d., 250 \pm 11 (n=11), 4-12m., 227 \pm 10 (n=24)]. All the mean Stimulated F from Treated were subnormal [147 \pm 11 (n=13), p<.01, 173 \pm 12 (n=20), p<.001, 187 \pm 7 (n=5), p<.05, respectively]. It is concluded that Synthetic Glucocorticoid treatments administered to mothers may induce relative Cortisol deficiencies in their newborns. This has to be taken into account especially in cases of obstetrical, neonatal stresses or of early surgery.

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148 LONG-TERM TREATMENT OF HYPOTHALAMIC-PITUITARY
CUSHING SYNDROME WITH o,p'-DDD IN
LOW DOSAGE.

3 children with Cushing syndrome aged 9 to 15 were treated with o,p'-DDD (Lysodren[®]) for 5 to 10 years. The drug lowers plasma cortisol by stimulating the microsomal enzyme system of the liver. In addition it has a direct cytotoxic effect on the adrenal cortex. Initial dosage was 25 - 45 mg/kg; maintenance dosage 15 - 20 mg/kg body weight. The treatment was monitored by measuring the plasma concentration of cortisol and o,p'-DDD and its metabolite o,p'-DDE according to needs. Clinical remission was achieved in 12 weeks. Good long standing clinical results with normal plasma cortisol, diminished cortisol response to ACTH, and without clinical side effects were obtained at a plasma concentration of o,p'-DDD of 5 to 10 μ g/ml. Under treatment one of the patients became pregnant and delivered a healthy newborn. It is concluded that o,p'-DDD in low dosage and additional gc determination of its plasma level allow to control Cushing syndrome over long periods of time without clinical side effects.