D. 1'Allemand \*, A.Grüters, \* P. Heidemann, M.Hasala \*, B. Weber Depts. of Pediatrics, Free University Berlin and University of Göttingen, F.R.G. SUCCESSFUL METYRAPONE (M) TREATMENT FOR CUSHING'S DISEASE

( C D ) IN AN ADOLESCENT BOY.

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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~ -dihydro-F were increased (86.4 and 370,40/ 24h). C T-scans of pituitary and adrenals were unconspicuous. Normal A C T Hlevels (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 A C T H and C R F -via A C T H- indicated a central origin of hypercortisolism. 24h-secretion of gonadotropins was supp-ressed and hypopulsatile; H G H was reduced during sleep and after G H R H 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 mg/ml  $\pm$  37%) and D H E A S (4406 vs 3333 ng/ml); slight elevation of A C T H (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 renine activity and high somatomedin C were unchanged. Clinically the patient exhi-biteded catch-up growth and an increase of testicular volume without adverse M-effects.

Conclusion: If surgery is not feasible, M may be an effective longterm 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  $(32.3 \pm 5 \ \mu\text{g/d1})$  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; HCH, 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 HCH, caused by the hypercortisolism.

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CUSHING'S SYNDROME, IDENTIFICATION OF ACTH SOURCE BY SELECTIVE CATHETERIZATION AND ACTH AND A-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 /3-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 ug/1.73 m<sup>2</sup>. 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), tumorside 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  $\triangle$  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 outmost importance, especially in the pediatric age group.

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146 Kolding Hospital, Dept. of Pediatrics, Rigshospitalet, Copenhagen, Denmark. 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-groupexcretions are shown in mg/24 h compared to normals (N):

	AGE	<u>Σthf</u>	THS	Στήβ	P-triol	<u>∆-5-P-triol</u>	<u>17ks</u>	16-0H-DHA
н	5	16.9	0.6	1.6	0.6	<0.1	o.7	<0.1
	8	14.4	0.5	0.6	1.0	0.1	o.l	<o.1< td=""></o.1<>
	10	10.3	с.4	1.6	0.5	<0.1	1.1	<0.1
	12	9.7	0.4	0.9	0.9	<0.1	1.6	<o.1< td=""></o.1<>
MD	4	6.2	0.8	1.7	<o.1< td=""><td><o.1< td=""><td>0.9</td><td><o.1< td=""></o.1<></td></o.1<></td></o.1<>	<o.1< td=""><td>0.9</td><td><o.1< td=""></o.1<></td></o.1<>	0.9	<o.1< td=""></o.1<>
A	4	9.0	0	1.3	0.3	0	0.5	<o.1< td=""></o.1<>
	10	8.9	0.7	<0.2	o.3	<o.2< td=""><td>0.4</td><td>&lt;0.1</td></o.2<>	0.4	<0.1
С	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	31.3
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<0.01 <u>N (14 (3.6 (0.3 (1.2 (0.5 (0.2 (2.0 (0.01)))))</u> The excretion of total cortisolmetabolites ( $\Sigma$ THF) was increasing in the order of MD < A < H < C, THS in order of H < A < MD < C. P-triol,  $\Delta\text{-}5\text{-}P\text{-}triol,$  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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( Introd. by F.Girard ). Lab. Explorations Fonctionnelles, Hôpital Trousseau, 75012, Paris, France. CORTISOL ASSESSMENT OF BABIES BORN FROM

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CORTISOL ASSESSMENT OF BABLES BORN FROM MOTHERS TREATED BY GLUCOCORTICOIDS Basal and stimulated (IM .125 µg of short-acting Synacthen) Cortisol (F) levels were evaluated in 34 bables (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 agematched <u>Control</u> 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 <u>Controls</u>, 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±7 ng/ml (mean±SEM) normally increase of Basal F to 93±7 ng/m1 (meanISEM) hormanly observed. Stimulated F from Controls reached identical values whatever the age group considered  $[0-6 d., 208\pm8 (n=4); 7-90 d., 250\pm11 (n=11), 4-12m.,$  $227\pm10 (n=24)]$ . All the mean Stimulated F from Treated were subnormal  $[147\pm11 (n=13), p<.01, 173\pm12 (n=20), p<.001, 187\pm7 (n=5), p<.05, respectively]. It$ is concluded that Synthetic Glucocorticoid treatments administered to mothers may induce relative Cortisol deficiencies in their newborns. This has to taken into account especially in cases of obstetrical, neonatal stresses or of early surgery.

E. Keller<sup>x</sup> R. Benecke<sup>x</sup>, B. Vetter<sup>x</sup>, H. Willgerodt<sup>\*</sup> (Introd. by P. Rochiccioli). Karl-Marx-University, Leipzig, GDR. LONG-TERM TREATMENT OF HYPOTHALAMIC-PITUI-TARY CUSHING SYNDROME WITH o,p'-DDD IN 148 LOW DOSAGE.

3 children with Cushing syndrome aged 9 to 15 were treated with o,p'-DDD (Lysodren  $^{\rm R}$ ) 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 corit has a direct cytotoxic effect on the adrenal COT-tex. Initial dosage was 25 - 45 mg/kg; maintenance dosage 15 - 20 mg/kg body weigth. The treatment was monitored by measuring the plasma concentration of cortisol and o,p'-DDD and its metabolit o,p'-DDE ac-cording to needs. Clinical remission was achieved in 12 weeks. Good long standing clinical results with nearent plasma cortisol diminished cortisol response. 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 10µg/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 addi-tional gc determination of its plasma level allow to control Cushing syndrome over long peroids of time without clinical side effects.