117 PRENATAL TREATMENT OF A GIRL WITH 21-HYDROXYLASE DEFICIENCY (CAH). Dietrich Knorr, Frank Bidlingmaier, Helmut G. Dörr and Ursula Kuhnle. Children's Hospital, University of Munich, Munich, FRG.

The possibility of prenatal diagnosis of CAH by steroid determinations and HLA typing in amniotic fluid and the knowledge that Dexamethasone (Dexa) crosses the placental barrier induced attempts on prenatal treatment of CAH girls by giving the mothers Dexa during pregnancy. The question is when to start treatment. Androgens start to act at week 8 of gestation, but it is still under discussion whether the fetal adrenals are under hypophyseal control before week 20.

We treated the mother of a severely virilized CAH girl during her second pregnancy. We gave Dexa (0.5 mg/d) from week 12 to week 15, stopped for 7 days before amniocentesis, and then continued treatment until delivery. The fetus was diagnosed to be female and homozygous for CAH. Pregnancy and delivery were uncomplicated. The treated girl was virilized to the same degree as her untreated sister; however, clitoromegaly was markedly less developed (2cm in length vs 4cm in the untreated child). Adrenal steroids were elevated slightly in umbilical vein and artery, but highly in plasma at day 5 of life.

We see three possible explanations for the fact that virilization was influenced not qualitatively but only quantitatively by prenatal treatment:

1. the dose of Dexa may have been too low;
2. treatment may have started too late;
3. the activity of the fetal adrenals possibly is not influenced by Dexa at the time when early steps of virilization take place.

118 CONGENITAL ADRENAL HYPERPLASIA (CAH) MONITORED BY SERIAL 17OH-PROGESTERONE (17P) DETERMINED IN 3 MATRICES. Ieuan A. Hughes, Janet Robinson, Jeffrey Dyas, Richard F. Walker and Diane Riad-Fahmy. University of Wales College of Medicine, Dept. of Child Health and Tenovus Institute, Cardiff. UK.

A blood spot (BS) assay was developed for use in infants to supplement plasma/saliva 17P assays used to monitor older CAH children. 17P recovery from a 6 mm blood disc immersed in ethanol, eluted with buffer and solvent extracted was >95%. A magnetised solid-phase antiserum and ^{125}I-tracer was used as in the routine 17P assay. Sensitivity was 1.5 pg/tube (0.5 nmol/L). Simultaneous plasma, saliva and BS samples were collected 1-2 hrly for 12-24hr from treated patients. Profiles of 17P in all 3 matrices was identical, whatever the control (r=0.99). Weekend profiles of BS and saliva 17P in samples collected at home are shown in the Table (means of 2 daily profiles).

TREATMENT	0800 BS (mmol/L)	0800 Saliva (pmol/L)	1200 BS	1200 Saliva	1800 BS	1800 Saliva	2200 BS	2200 Saliva
UNDER -	500	11,000	278	4000	92	2500	50	820
OVER -	11.6	118	2.5	190	1.9	120	0.5	<100
ADEQUATE -	59	1,200	24.8	1000	18.0	700	3.2	400

BS and saliva 17P values indicated the degree of control, identified over-treatment and again showed a diurnal rhythm in the under-treated. Selective use of plasma, BS and saliva 17P measurement now permits detailed monitoring of CAH at all ages.

119 CLONING AND STRUCTURE OF THE BOVINE 21 HYDROXYLASE GENE. Bon-chu Chung, Karla J. Matteson, and Walter L. Miller, University of California, San Francisco, Department of Pediatrics, San Francisco, CA, USA

21 hydroxylase is a single specific 49000 dalton microsomal cytochrome P450 termed P450c21. Using two chemically synthesized oligonucleotide probes, we screened a bovine genomic DNA library, and identified a phage, λE11, carrying the gene for P450c21. The identity of λE11 was proven by initiating dideoxy sequencing from the two oligonucleotides directly on the full-length, uncleaved phage template. Hybridization of total bovine genomic DNA to λE11 restriction fragments indicates some DNA in or near the P450c21 gene contains repetitive sequences. Northern blots indicate the primary gene transcript is 6.8 to 9.5 kb long and that the mature mRNA exists in two principal forms of about 2.2 and 2.4 kb in length. Southern blots indicate there are two copies of the gene in the bovine genome. Sequence analysis of a 1141 bp EcoRI fragment of the gene shows three complete exons and a portion of a fourth exon. The intron/exon arrangement is similar to that seen for the P450c gene induced in liver by 3-methylcholanthrene but not to that of the P450e gene induced by phenobarbital. This sequence analysis correctly determines the amino acid sequence of 148 amino acids of this important enzyme. This cloned 1141 bp fragment cross-hybridizes to human genomic DNA indicating it is a useful probe for studying the human P450c21 gene in patients having 21 hydroxylase deficiency.

120 PRIMARY PIGMENTED NODULAR ADRENOCORTICAL DISEASE. RARE CAUSE OF THE CUSHING SYNDROME. J. Aidan Carney, Mayo Clinic, Department of Pathology, Rochester, MN

Five patients (three females and two males, ages 12-21 years) had clinical features of the Cushing syndrome. Results of biochemical studies (in four patients tested) suggested the presence of an autonomously functioning adrenocortical neoplasm. However, radiologic examination of the adrenals did not show an adrenal tumor. The five patients underwent curative bilateral total adrenalectomy and did not manifest the Nelson syndrome postoperatively (follow-up, 0.5-22 years). The adrenal pathologic findings in these patients were similar. Gross findings included: 1) decreased, normal, or slightly increased total gland weight; 2) studding of the external and cut surfaces by small (<4 mm) black, brown, dark-green, red, or (rarely) yellow nodules; and 3) cortical atrophy and disorganization of the normal zonation between the nodules. Microscopically, the nodules were composed predominantly of enlarged, globular, cortical cells with granular eosinophilic cytoplasm that often contained lipofuscin. Twenty-six similar cases have been reported or communicated to us. Findings in these plus our five cases identify a special type of adrenocortical pathology associated with Cushing syndrome, for which we suggest the name "primary pigmented nodular adrenocortical disease." There were three instances of familial involvement. Associated conditions include myxomas (cardiac, cutaneous and mammary), spotty pigmentation (cutaneous and mucocutaneous) and other types of endocrine overactivity (sexual precocity and gigantism).

121 RECURRENCE OF CUSHING'S DISEASE AFTER PITUITARY DISEASE. J DIMARTINO, E STONER, M CAPPA, S PANG, J TEMECK, MI NEW, The New York Hosp-Cornell Med Ctr, Dept Pediatrics, New York NY 10021

We report a 10 year old female with Cushing's disease with recurrent disease 5 yrs after successful pituitary irradiation. At presentation, bone age, skull films, head CT and visual fields were all normal. Basal serum F, urinary 17-OHCS, free cortisol (F), and 6β-hydrocortisol (6β-OHF) were elevated. Serum F lacked circadian variation and was partially suppressed by high dose dexamethasone (dex). She received pituitary irradiation with a cumulative dose of 4,000 rads over a 1 month period. Serum F, 17-OHCS, 6β-OHF, urinary free F returned to normal, growth velocity improved, and puberty ensued with menarche occurring 3 yrs after irradiation. However, lack of diurnal variation of F persisted. Despite radiotherapy, five years later she developed clinical and biochemical evidence of mild recurrent Cushing's disease. Bone age, head CT, visual fields, and TRH, LHRH and L-DOPA/glucagon testing were all normal. Morning cortisol, 17-OHCS, and 6β-OHF were elevated and were partially suppressed only after high dose dex. The 8:00 PM ACTH level was elevated to 40 pcg/ml. After ovine CRF administration the maximum ACTH response was 46 pcg/ml; the ACTH concentration is increased and the absent ACTH response to CRF is abnormal. In patients with Cushing's disease treated with radiotherapy, the ACTH response to CRF stimulation may not be reliably compared to that of normal controls.

Conclusion: Therefore Cushing's disease may recur despite successful pituitary irradiation. This suggests a hypothalamic CRF producing lesion as the primary lesion in Cushing's disease.

122 BROMOCRIPTINE TREATMENT FOR CUSHING DISEASE UNDER THE FORM OF INTERMEDIATE LOBE DISEASE. Thomas E. Romer, Anna Wolska, Jerzy Klimaszewski. Child's Health Center, Warsaw, Poland.

In two cases of Cushing disease diagnosed on the basis of clinical symptoms and laboratory findings with abolished circadian cortisol rhythm the following test were performed: I.V. bolus TRH and LH-RH tests with serum ACTH radioimmunoassay and I.V. infusion cortisol suppression test according to Fehm et al. In female patient A.P., 11 years old, a brisk increase of serum ACTH after LH-RH was noticed, in male patient G.C., 17 years old, increase of serum ACTH after TRH was stated. On the basis of this tests an "intermediate lobe disease" was diagnosed. Additionaly in patient G.C. a paradoxical increase of ACTH during the cortisol infusion, was observed. On the treatment /Parlodel 7 mg/day/ a prompt release of symptoms and a significant growth acceleration in both patients were observed. The growth rate in patient G.C. before treatment was 0,8 and during treatment 3,1 cm/year and in patient A.P. 1,8 and 5,8 cm, respectively. As intermediate lobe is under dopaminergic control, response to bromocriptine seems to confirm the intermediate lobe disease in our patients. Authors conclude that bromocriptine treatment can be successful in Cushing disease under the form of intermediate lobe disease as diagnosed on the basis of TRH and/or LH-RH tests.