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PHARMACODYNAMIC RESPONSE OF 17OH-PROGESTERONE (17P) TO ACUTE DEXAMETHASONE IN CONGENITAL ADRENAL HYPERPLASIA (CAH).

Dexamethasone (Dex) produces an unpredictable adrenal suppressive response in CAH patients. Maintenance steroid therapy was stopped for 48h in 11 patients (14-21 yr) with 21-OH deficiency. Each then received 0.01 mg/kg boluses of Dex I.V. and orally on consecutive days at 0900 h. Plasma 17P and Dex levels were measured every 10 min. for the first hour, then hourly for 24h on each occasion. Dex elimination half life ($t_{\frac{1}{2}}\beta$ Dex) was 2.18 - 4.50h (mean 3.53). Mean plasma 17P pre-I.V. Dex (17P max) was 331 nmol/l (42-565); individual values were inversely proportional to adequacy of control on maintenance therapy. Both I.V. and oral Dex caused an immediate and exponential fall in 17P to produce complete cessation of adrenal 17P secretion followed by natural 1st order elimination of 17P from plasma. $t_{\frac{1}{2}}\beta$ 17P was 1.93 - 2.93h (mean 2.55). Satisfactory 17P levels (< 30 nmol/l) were achieved up to 13.2h (mean 8.2) after a Dex dose. 17P levels were maintained for a period (P) ranging from 16-20h (mean 18h) until a sharp rise at night. $t_{\frac{1}{2}}\beta$ Dex did not correlate with P; the former value (mean 3.53h) predicts <3% Dex dose remaining after 18h. A single morning dex dose (0.01 mg/kg) causes complete suppression of daytime 17P values but when 17P increases again depends on 17Pmax at time of dose, $t_{\frac{1}{2}}\beta$ 17P and 17P circadian rhythm periodicity; the last 2 parameters are unique to each patient.

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LARGE SCALE PHYSICAL MAPPING OF THE REGION SURROUNDING THE ADRENOLEUKODYSTROPHY GENE

Adrenoleukodystrophy (ALD) is an X-linked genetic peroxisomal disorder in which phenotype may be strictly limited to Addison's disease. Though there is circumstantial evidence that the primary defect involves lignoceryl-CoA-synthetase, the precise gene involved has not yet been identified. Both ALD and red/green color blindness (CBD) have been mapped to the distal long arm of the X chromosome (Xq2-8). We have studied 13 French ALD kindreds and found visual pigment genes reorganization and/or deletion in 8 of 13 kindreds (60%) as opposed to the 8% expected. Such changes may reflect chromosomal events underlying both ALD and CBD genes. A physical map is clearly needed to understand the reorganization of this region in ALD patients and will constitute a first step to approach the ALD gene by "chromosome walking" or "jumping". High molecular weight genomic DNA digested with a number of restriction enzymes that cut infrequently was separated by pulse field gel electrophoresis and hybridized to cDNA and anonymous genomic probes that derive from Xq2-8. Preliminary results suggest that ALD gene lies between coagulation Factor VIII and CBD genes at a distance of less than 150 kb from CBD.

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EVIDENCE FOR RECOMBINED HAPLOTYPES IN THE AREA OF THE 21-HYDROXYLASE (21-OHase) A- AND B GENE IN CONGENITAL ADRENAL HYPERPLASIA (CAH)

The 21-OHase is encoded by 2 genes located in the HLA major histo compatibility complex on chromosome 6. While the 21-OHase B gene, corresponding to the 3.7 kb endonuclease Taq I fragment, is functional, the 21-OHase A gene, corresponding to the 3.2 kb Taq I fragment, is a pseudogene.
Using a relatively short 0.235 kb probe recognising the first 2 exons of the 5'end of both genes, we analysed genomic DNA of 12 patients with salt-wasting CAH, after digestion with 4 different restriction enzymes.
9 out of 12 patients showed a change of normal molecular organisation: In 2 siblings and 3 other unrelated patients, we found a normal Taq I pattern but, at the same time,the loss of the A genc specific Hind III fragment. Another patient showed an increased B gene signal in the Taq I digest,whereas in the Eco R I digest the A gene signal was increased. Two HLA identical siblings, one with mild, the other with severe CAH, both surprisingly showed homozygous loss of the 3.7 kb Taq I fragment. However, Eco R I digest revealed that the B gene specific recognition sites were preserved.The same occured in another unrelated patient.
We infer frequent exchange between the 2 neighbouring 21-OHase A and B genes by either unequal crossing over or gene conversion resulting in hybrid genes that carry A- as well as B gene specific recognition sites in the gene or its' surrounding districts.

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EFFECTS OF PUBERTAL MATURATION AND LONG TERM EXPOSURE TO TRIPTORELIN ON FREE TSH ALPHA-SUBUNIT RELEASE IN FEMALE SUBJECTS.

The release of the free TSH α-subunit (F-TSH-A) during TRH stimulation (200 µg IV/m2) was investigated in 8 prepubertal girls (4-9 years of age, group I), 8 girls with precocious puberty (4-8 years of age, pubertal stages 2-3, group II) and 12 menstruating women (group III). F-TSH-A was measured by a polyclonal RIA. Results were expressed as mean ± SEM (ng 1°-IRP-hCGα/ml). Basal values in group I, II, III were respectively 0.14 ± 0.02, 0.33 ± 0.08 ($p = 0.02$) and 0.47 ± 0.05 (not different from II). TRH peak values were respectively 0.59 ± 0.12, 0.75 ± 0,08, and 0.71 ± 0.06 (differences not significant). The increment between basal and peak values was significantly higher ($p < 0.02$) in group I (0.45 ± 0.07) than in group III (0.24 ± 0.03). Girls from group II were treated by IM injections every 4 weeks of the LH-RH agonist triptorelin (Decapeptyl microcapsules, 60 µg/kg body weight). After 6 months basal and peak levels increased respectively to 1.1 ± 0.12 and 2.0 ± 0.20 ($p < 0.001$ relative to pretreatment values). The increment (0.84 ± 0.11) was significantly higher than in groups I, untreated II and III. These data suggest that : 1-ovarian secretion might exert a suppressive effect on the release of F-TSH-A ; 2-long term LH-RH agonist administration might increase α-subunit secretion not only by the gonadotroph cells, but also by the thyreotroph cells, provided a direct effect of TRH on the gonadotrophs can be precluded.

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DRASTIC REDUCTION OF NEWBORN GOITRE FREQUENCY 2 YEARS AFTER IODINE PROPHYLAXIS IN THE TOWN OF JENA/DDR

In a district of an iodine-deficient area with an average goitre frequency of 4.7% (n=15 904) in the years 1976-1982 low BEI values (<4.0 µg%) were measured in 93 out of 154 (60.4%) newborns with goitre, a retarded bone age was evident in 58 out of 118 cases (49.2%). Following salt iodination (25mgKI/kg salt since 1983 and 32mg KIO_3/kg since 1985) a reduction in goitre frequency from 3.4% in 1982 (n=2811) to 1.0% in 1985 (n=2656) and after introduction of an additional iodination of animal feed mineral mixtures in 1986 to 0.1% and 0,15% took place in 1986 and 1987, resp.(n=5337). Urinary iodine excretion increased in newborns without goitre from 10.6±6.6 in 1982 (n=38) to 45.3±36 µg/l(n=12) in 1987 during the 5th day of life,in mothers from 19.3±7.4 µg/l (n=57) to 64.6-30 µg/l(n=32) on the 5th day p.p. In mother's milk only a slight augmentation was measured on the 5th day p.p.(13.6±8.2 µg/l, n=57 to 19.2±7.6 µg/l, n=33). It is concluded that under the country-wide used iodination system the iodine supply to the fetus by pregnant mothers is sufficient to prevent newborn goitres and in this way transient hypothyroidism in the newborn age.

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DETECTION OF THYROID TISSUE BY THYROID ECHOGRAPHY (TE) FOR THE DIAGNOSIS OF CONGENITAL HYPOTHYROIDISM (CH) IN SCREENING-POSITIVE BABIES.

Discrepancies between the results of TE and thyroid scintigraphy (TS) in congenital hypothyroid infants have been previously reported. In previous studies TE systematically detected structures in the physiological position of the thyroid gland also in agenetic babies, therefore not confirming the diagnosis of hypothyroidism. We have examined 29 infants detected by neonatal screening for CH, referred to our Endocrine Unit to confirm the diagnosis. In the first day a complete evaluation of thyroid endocrine function and TE were performed (the operator ignored the suspected diagnosis). In the second day the infants underwent TS and the L-T4 replacement therapy was started. Results:

	AGENESIS	ECTOPIA	HYPOPLASIA	NORMAL GLAND	CONFIRMED DIAGNOSIS
TS	16	11	2	0	100%
TE	24	3	2	0	100%

Conclusion: TE confirmed in all cases (100%) the presence of thyroid abnormalities consistent with hypothyroidism, justifying the immediate beginning of L-T4 therapy, even if not discriminating between agenesis and ectopia (which is not essential in the therapeutical approach). Therefore we believe that TE, a non invasive tool, is useful in most cases in excluding transient hypothyroidism and false positives, confirming thyroid abnormalities even if not discriminating between agenesis and ectopia.