9 Reverse Triiodothyronine (RT_3) Levels In Paired Arterial And Venous Cord Blood Are Consistent With Greater Inner Ring Deiodoination of Thyroxine (T_4) On The Venous Side.

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Paired arterial and venous cord blood samples were obtained from 29 normal newbrons (15 M & 14 F). T_4 & TBG were determined for all and additionally other indices were determined as follows T_3 in 27 (14 M & 13 F), RT_3 in 16 (8 M & 8 F), thyroglobulin (Tg) in 14 (7 M & 7 F) and TSH in 11 (5 M & 6 F).

No sex difference in thyroid indices was found. Arterial and venous cord serum thyroid indices correlated positively (T_4, r=0.673, TBG, r=0.752, T_3, r=0.909, RT_3, r=0.913, Tg, r=0.934, & TSH, r=0.989, p<0.005). The differences between the means ± SD of arterial and venous levels was significant (p<0.05) only for RT_3 (203 ± 43.3 vs 237 ± 61 ng/dl). Arterial (T_4 vs T_3, r=0.451 p<0.01 & T_4 vs RT_3, r=0.566, p<0.025) and venous (T_4 vs T_3, r=0.627, p<0.005 & T_4 vs RT_3, r=0.628, p<0.005) T_3 and RT_3 levels correlated positively with T_4 levels. In contrast, arterial (r=0.104, p>0.3) and venous (r=0.115, p>0.3) T_3 and RT_3 levels did not correlate significantly.

These data are in keeping with the reports that suggest that placental inner ring deiodination of maternal thyroxine is a source of fetal RT_3. The findings support the suggestion that placental inner ring deiodination of T_4 and T_3 may be the mechanism responsible for the failure of maternal T_4 and T_3 to cross the placenta.

10 NUCLEAR T_3 RECEPTORS OF LYMPHOCYTES IN THYROID HORMONE RESISTANCE (THR).

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The interaction of thyroid hormones with specific nuclear receptors in target cells is generally thought to be the site of initiation of hormone action. We investigated nuclear triiodothyronine (T_3) binding in lymphocytes of 4 patients with partial generalized THR. The patients had a chronological age of 3.5, 13, 2.3 and 26 years, respectively, were clinically euthyroid and exhibited goiters of different sizes. Total and free thyroxine (T_4) and T_3 were significantly elevated in the presence of inappropriately increased TSH. The mode of inheritance was autosomal dominant in patients III and IV (father and son).

	I	II	III	IV	controls
TT_4 (µg/dl)	23.4	19.1	14.5	20.3	4.7-13.2
FT_4 (µg/dl)	4.4	4.4	2.4	3.3	1.0- 2.1
TT_3 (ng/ml)	3.0	3.8	2.3	2.9	1.3± 0.4
FT_3 (pg/ml)	10.7	>13.2	15.9	13.2	2.2- 6.8
TSH (µU/ml)	12.2	0.4	8.7	5.2	< 4.0
Ka ($10^9 M^{-1}$)	0.4	0.08	0.1	0.48	0.96±0.17

Affinity constants (Ka) derived from Scatchard analyses of the T_3 binding data were significantly decreased in the patients compared to controls. Our data suggest that THR is caused by a defective receptor affinity for T_3. They are in contrast to published data (JCEM, 55, 502, 1982). Biochemically, THR seems to be a heterogeneous disorder with receptor and post-receptor defects.

11 KETOCONAZOLE THERAPY IN LHRH ANALOG RESISTANT PRECOCIOUS PUBERTY.

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Three boys with familial gonadotropin-independent precocious puberty(Rosenthal et al,JCEM 57:571,1983) were treated with LHRH analog for periods of 1-4 mos,without clinical or biochemical response.The effects of the antifungal drug ketoconazole were studied in these boys prompted by the observation that this agent may interfere with testosterone biosynthesis.With 200 mg/12 h P.O. there was an immediate significant fall in serum testosterone(T) from a pre-Rx level of 7.0±1.6 nM/L (mean±SEM) to 1.3±1.1(P<0.05),with a reciprocal rise in 17-OHP from 2.3±1.5 to 7.2±1.1 nM/L.DHAS and androstenedione levels were unchanged.The T response to hCG remained intact. Major improvement in behavior, linear growth & skeletal maturation were sustained for the duration of treatment. *cm/yr

Pat	Pre Rx				Duration Rx	Post Rx		
	(yrs)	BA	Ht vel*	ΔBA/ΔCA	(mos)	BA	Ht vel*	ΔBA/ΔCA
1	4.2	8	17	1.9	13	9	7.0	∿1
2	5.3	8	11	1.51	9	9	6	∿1
3	4.0	9.5	17	2.25	9	10	4.8	∿1

The cortisol response to $ACTH^{1-24}$ was significantly blunted after 5 days of Rx,but returned to normal after 1 mo with normal diurnal rhythm.Hepatic abnormalities were not observed in up to 13 mos of treatment.We conclude that ketoconazole may provide effective long-term control of precocious puberty in males through C 17-20 lyase inhibition,and speculate that this drug may play an important therapeutic role in other conditions of androgen excess

12 A DOUBLE BLIND PLACEBO CONTROLLED (dbpc) STUDY OF LHRH TREATMENT OF UNI-& BILATERAL CRYPTORCHIDISM.

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250 prepubertal boys were treated with LHRH nasal spray (HOE 471) 400 ug t.i.d.; 28 days in dbpc study. Whenever a 2nd Rx course proved unsuccessful after a 4wk interval, orchidopexy was performed. Complete descent: group (gr) a (age 1-2 yrs, 37 boys) 4/41 testes (10%); gr b (age 2-6 yrs, 85 boys) 16/97 testes (16%) gr c (age 6-12 yrs, 91 boys) 48/118 testes (40%). 8 testes descended during placebo Rx. 30 testes needed 2 Rx courses. Relapse in 9 testes. An additional Rx course successful in 5 testes. Surgical findings in 139 boys: Passed through the inguinal canal but obstructed with processus vaginalis closed or narrow canal: gr a: 40%; gr b, c: 65%. Wide open processus vaginalis with 50% major epididymal deformities: gr a: 40%; gr b, c: 27%. No testes: gr a: 16%; gr b, c: 8%. Hormonal data: Before Rx: Testosterone(T) response to 1500 U HCG i.m. (gr a>gr b>gr c; p<0,05) was similar in all groups compared to age matched controle (amc) n=61. Basal LH/FSH values and only the LH response to LHRH 50 ug i.v. were higher in gr a-c compared to amc (p≤0,05). After Rx: LH response decreased only in gr a, FSH response decreased in all groups, but only significantly in b and c (p<0,05). No change in basal T values b and a Rx in gr a-c. No hormonal differences were found between uni- and bilateral cryptorchidism nor in success and failure groups. We conclude that the major anatomical abnormalities and lowest success rate to hormonal Rx were found in gr a (1-2 yrs). Our hormonal data do not support the theory that the mode of action of LHRH Rx is thru activation of the pituitary gonadal axis.

13 ANTIGONADOTROPIC-CELLS ANTIBODIES IN THE SERUM OF CRYPTORCHID CHILDREN AND INFANTS AND THEIR MOTHERS.

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An indirect immunofluorescence test revealing serum antibodies directed against human and guinea pig pituitary gonadotropic cells (AGC-A) was used in 46 cases of common cryptorchidism, 26 unilateral and 20 bilateral, without associated abnormalities. Among 23 patients aged 1 to 11 years, 14 had AGC-A, without correlation with age, uni or bilaterality, or the results of further hormonal investigations using LHRH and hCG stimulation tests. No AGC-A were found in 24 control boys of same ages. Among 23 cryptorchid infants aged 1-3 months, 12 had AGC-C, without correlation with their plasma levels of testosterone, LH and FSH; follow-up in 9 showed that AGC-A persisted in 7, disappeared in 2. Paired study was done in 15 newborns and mothers and was concordant in 14, 7 with and 7 without AGC-A. In spite of the discrepancies, the study of auto-immunity could improve the understanding of congenital testicular maldescent.

14 THE INHIBITION OF SEXUAL MATURATION BY MELATONIN IN THE MALE RAT MAY BE MEDIATED BY AMPLIFICATION OF THE OPIATERGIC NEGATIVE CONTROL OF LH SECRETION

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Our group has shown that daily administration of melatonin (MT) markedly delays sexual maturation in the male rat (Endocrinol. **112**,1578,1983 and **115**,2303,1984). In this study, we have evaluated the level of tonic inhibition by opiates in normal **40-day old** rats, and in rats with delayed sexual development induced by daily MT (100 ug) injection between 20 and 40 days. Naloxone (NAL) s.c. injection (2.5 mg/kg) produced a significant increase of plasma LH in normal rats, **not seen in MT-treated rats.** Injection of morphine sulphate (MS) or of the potent Met-Enkephalin analog FK-33-824 (FK) inhibited LH secretion in control rats. In MT-treated rats, the low plasma LH levels were not affected by opiates. Pretreatment with MS, or with the FK agonist prevented the NAL-induced rise of LH in rats not treated with MT. Plasma PRL levels were decreased after NAL both in untreated- and MT-treated rats. In keeping with the observation that MT no longer inhibits sexual functions in **adult** rats, LH response to NAL was normal in adult rats that have been treated for 20 days with MT. These results demonstrate that MT may potentiate or mimic the tonic inhibition of LH secretion exerted by endogenous opiates during sexual development. They reinforce the concept that modulation of opiate control is important for the progress of sexual development.