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VARICOCELE (V) IN CHILDHOOD AND ADOLESCENCE (VCA). EFFECT ON TESTICULAR GROWTH AND HORMONAL MILIEU.

The relationship of VCA to future infertility remains enigmatic. Current quidelines for surgery on VCA are based on fragmentary knowledge. In order to delineate the natural history of VCA, neccessary to establish criteria for surgery, we initiated a longitudinal study 2 years ago. Base-line data (clinical, hormonal), and data on sonography (S) are herein reported. 1395 pupils, aged 6-17 years, were examined. 111 cases of V were detected, 98% cited on the left testis. The incidence of V increased from 1.6% at age 6 years to 20.6% at age 14 and declined to 4.8% at age 17. The same trend was noted when data were expressed according to testicular volume (2-3ml:2.7%, 10-12ml:26%, 20ml:4.2%). This decline was not observed in V grade III. Values of testosterone, DHEA-S, E_2 and the 60 minutes response of LH and FSH to IV LHRH did not show any difference between subjects with grade I and III V. The Δ volume (R-L testis) of the affected subjects, estimated with the orchidometer or S, did not differ from controls. However 20% of VII-III had Δ volume R-L testis > 3ml by S. Although preliminary, these date indicate that 1) The incidence of VCA is high, 2) Some V grade I and II are resolved with advancing puberty, 3) No reflexion of the V on the hormonal parameters, examined thus far, was detected, 4) No adverse effect of V on testicular growth was noted in the total group. However 20% of VII-III had Δ volume R-L testis > 3ml by S, 5) The long term follow-up of V subjects will determine the natural history of V and most likely define criteria for surgery.

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TESTICULAR FUNCTION AFTER TESTOSTERONE TREATMENT IN TALL ADOLESCENTS

Testosterone treatment in tall boys is widely used to reduce predicted adult height. But there are only few data on testicular function after discontinuation of therapy. We studied 21 young men (22 ± 2.8 yrs. of age) by LH-RH-test and analysis of spermatic fluid 1-12 yrs. after therapy. LH (1.79 ± 0.72 µg/l and FSH (0.78 ± 0.9µg/l) could be stimulated by LH-RH-test up to peak levels of 8.54 ± 3.83 and 1.7 ± 1.59 µg/l, respectively. 5 of 21 men showed pathological results. Mean testicular volume was 25.3 ± 7.6 ml but ranged from 10 to 40 ml. Results of spermatic fluid analysis are shown in the table. 4 of 19 sperm counts were below a normal limit of 20 mio./ml. Further criteria applied for evaluation of sperm quality increased the percentage of pathological conditions up to 50 %.

These findings suggest consequences for testicular function and reproduction, if supraphysiological doses of testosterone are administered to pubertal boys for reduction of predicted height.

	amount in ml	pH	sperm count in mio	% total motility 0'/60'	round cells in mio	normal morphol. in %	fructose content in µg/ml
X	2.9	7.4	67.3	60/60	4.0	53	2708
SD	1.1	0.2	58.6	9/ 9	3.3	13	1555
Mx	5.4	7.7	256.0	70/75	10.3	78	5890
Mn	0.7	7.0	2.1	30/35	0.3	35	400
norm	2-5	7.2-7.8	>20	>60	<6.0.	>50	>1200

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ESTIMATION OF THE EFFECT OF TESTOSTERONE (T) ON PROTEIN METABOLISM USING 15N

In 7 boys with short stature aged 11 years 9 month to 14 years 10 month growth hormone secretion was estimated by provocative stimuli after T-priming. By that occasion the influence of T on protein metabolism using 15N-tracer technique was investigated. 10 mg T/m^2 body surface area was administered daily for 5 days. On the 3rd day 13.5 mg /15N7 glycine per kg body weight were given orally and urine was collected for the following 3 days. The results of the excretion of 15N and total N in urine were calculated using a 3 pool model and compared with a basal period of 3 days after application of /15N7 glycine but without T.T-administration resulted in an increase of the rate of protein synthesis from 0.677 ± 0.37 mmol N/kg·h (M±SD) to 1.47 ± 0.37 mmol N/kg·h ($p < 0.001$) and of the N-flux from 1.28 ± 0.54 to 1.64 ± 0.42 mmol/kg·h ($p < 0.05$). The protein utilization increased from 51 ± 9.3% to 67 ± 7.6 % ($p < 0.01$), while the conventional whole N-retention, estimated without using 15N, did not change significantly. The results clearly demonstrate the advantage of 15N-tracer studies for investigating the metabolic effects of T.

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THE ASSESSMENT OF GONADAL FUNCTION IN XXY AND XYY BOYS USING SERIAL SALIVARY TESTOSTERONE SAMPLING.

Salivary Testosterone (ST) levels have been measured in boys from the Edinburgh Longitudinal Growth Study. 84 controls (46,XY) aged 7-16 yrs, 7 47,XYY and 16 47,XXY boys (aged 6-19 yrs) identified by cytogenetic screening of the newborn, collected six samples over one day (9am-9pm) for 4 months, then 8 and 16 months later. ST concentrations were measured by RIA# and correlated closely ($r=0.88$) with 18 matched plasma samples. Normal ranges were constructed by individual curve fitting. A diurnal rhythm was present prepubertally, but developed fully by G3 (9am +76%; 9pm - 32% of daily mean). ST profiles from the XYY boys did not differ from the controls. The mean ST level of prepubertal XXY boys (33.5pmol/l) was higher ($p<0.05$) than the controls (18.7pmol/l) and greater in those four boys with height velocity >90th centile (37.5pmol/l). 24 hour urinary adrenal androgen metabolites in these boys were analysed by GLC at Ninewells Hospital and were not elevated. The mean ST of 6 XXY boys at G5PH5 (119.8pmol/l) was lower than the normal range (149.3-235.4pmol/l). Four received oral testosterone undecanoate (TU). Repeating ST profiles allowed individual dosage adjustment (40-120mg daily). Early results show TU therapy to be associated with a reduction in skinfold thicknesses, but not to prevent transient gynaecomastia. Measurement of ST is a sensitive non-invasive method for serial monitoring of gonadal function.

#Walker RF et al. Int. J. Androl. 1980; 3: 105.

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GYNECOMASTIA IN THE PEUTZ-JEGHERS SYNDROME IS CAUSED BY TESTICULAR TUMOR AROMATASE PRODUCTION.

Gynecomastia was present in a 4 yr old boy without pubic hair or phallic enlargement but with growth acceleration, early pubertal testicular enlargement and a bone age of 8 yr. The patient and his father have Peutz-Jeghers syndrome. Testicular ultrasound showed diffuse disruption of the gonadal parenchyma in the patient but not in his father. Peripheral levels of testosterone (T), estradiol (E_2) and gonadotropins were prepubertal. Testicular vein blood samples revealed T levels of 680 and 690 pg/ml, 1/1000 the concentrations reported in adult men; in contrast, E_2 measurements of 1270 and 1150 pg/ml were similar to adult male levels, indicating increased T to E_2 synthesis. Testicular biopsies showed bilateral, multi-focal sex cord tumors with annular tubules. Aromatase activity assessed in tumor homogenates revealed the production of 422 pmol estrone/gm wet weight tissue/hr, two-thirds of the enzyme amounts found in human placenta. Aromatase was also detected by peroxidase-antiperoxidase immunocytochemistry using a specific monoclonal antibody and was localized within the cytoplasm of abnormal appearing Sertoli cells. In conclusion, increased tumor expression of a single enzyme resulted in excess steroid production (E_2) and symptoms thereof, without evidence of elevated substrate (T). Testicular aromatasomas are a unique cause of prepubertal gynecomastia.

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IN VIVO AND IN VITRO STUDIES OF A JUVENILE GRANULOSA CELL TUMOR.

A 16 month-old girl was seen for precocious puberty (breast, pubic hair). Plasma levels (ng/dl) of progesterone (P) (574-1830), 17OH-progesterone (OHP) (181-195) and estradiol (E2) (25-40) were in the range of an adult luteal phase. Androgens were moderately elevated. LH/FSH were suppressed. Dispersed cells were prepared from either luteinized (pool A) or interstitial (pool B) tumoral tissue. The secretory pattern was established after 1 day of culture and was similar to that in the cystic fluid of the tumor. Viability of the culture was checked by the maintenance of the steroid secretory pattern the next 3 days. On day 9th, the cells were stimulated by either hCG (10^{-9} M), FSH (1 ng), forskolin (FK) 10^{-5} M. cAMP (pmol) was measured after 1 h, OHP and P (ng) and E2 (pg) at 24 h. Results are given in the Table as mean production per 10^{-6} cells (*$p < 0.05$). Also, hCG receptors (sites/cell) were found but low in A (2800) and B (1400); FSH receptors were found only in A (940) on day 1 and were comparable on day 9.

	cAMP	P	OHP	E2		cAMP	P	OHP	E2
Control A=	0.59	69	0.8	136	B=	5.8	61	5.3	147
hCG	128	73	1.2	95		33	78	5.9	194
FSH	4.1	54	1.1	128		8.5	67	4.9	211
FK	1023*	133*	5.3*	192		513*	120*	7.5*	218
FK+hCG	2036*	129*	5.4*	144		1250*	122*	10.1*	237
FK+FSH	1662*	142*	5.3*	133		530*	130*	6.5	231

These studies show that the tumoral cells have a high autonomous steroidogenic activity, which was poorly stimulated by gonadotropins due to the low levels of receptors. However the adenylate cyclase and the steroidogenesis remained very sensitive to FK alone or associated with gonadotropin.