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PROGRESSIVE INCREASE IN NON-SEX HORMONE-BINDING GLOBULIN (SHBG)-BOUND TESTOSTERONE (T) FROM INFANCY TO LATE PREPUBERTY.

Sex hormones circulate in complex with two major serum proteins: SHBG and albumin (HSA). We have recently reported that there is a progressive decrease in the serum concentration of SHBG throughout male prepuberty. A computer program was used to calculate the distribution of serum T into SHBG-bound, non-SHBG-bound, HSA-bound and free fractions in 70 normal prepubertal boys, aged 0.5 to 12 y. The calculation was derived from the experimental measurements of serum T and SHBG assuming unique values for serum HSA and for the affinity binding constants. Non-SHBG-bound T, presumably the fraction of serum hormone that is available for transport into tissues in vivo, increased progressively from 1.44 $\pm$ 0.5 ng/dl ($\bar{X} \pm$ S.E.) at 0.5 y. to 10 $\pm$ 4.4 at 12 y. ($r=0.47$, $p < 0.001$), before any clinical signs of sexual development became apparent. Free T also changed in a similar fashion. These values can be compared with those of normal adult males (n=10) and females (n=7): 390 $\pm$ 63 and 12.7 $\pm$ 1.8 respectively. It is proposed that the gradually increasing androgen and estrogen milieu of the brain created by this mechanism might be of physiological significance in inducing the onset of puberty in normal boys.

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CLINICAL AND HORMONAL EVALUATION OF BOYS BORN WITH UNDESCENDED TESTES DURING THEIR FIRST YEAR OF LIFE

Forty-eight boys with uni- (n=40) or bilateral (n=8) cryptorchidism were followed during the first year of life with informed consent of the parents. 24 of them in study within the first 3 mo of life (<3 mo). Evaluation at 3,6,9 and 12 mo. LH-RH tests (100ug LH-RH i.v.) and basal testosterone (T) values were obtained at 3,6 and 12 mo. An HCG test (1500 IU HCG i.m.) with determination of T, dihydrotestosterone (DHT) and steroid precursors (P, 17OH-P, Δ 4, DHEA-S, 17OH-Preg) was performed at 12 mo of age. Age-matched control values were obtained in healthy children (C): T:n=144; LH-RH test: n=9; HCG test: n=7. RESULTS: 29 boys remained cryptorchid (gr I). In 19 boys (20 testes) a spontaneous descent occurred (gr II). Of the 24 boys in study < 3 mo spontaneous descent occurred in 12 boys (12 testes). From the age of 80 days on no significant differences could be found for transversal T, basal and peak LH and peak FSH serum values between gr I, II and C, nor for the same but longitudinal values between gr I and II. A positive correlation ($p=< 0.01$) was found between the basal LH/T ratio as well as peak LH/T ratio and age in gr I and II. No differences were found in gr I, II and C for basal and peak T, DHT, P, 17OH-P, Δ 4, DHEA-S and 17OH-Preg. WE CONCLUDE that spontaneous descent during the first year of life occurs in 40-50% of all cases. Our hormonal data do not support the theory of a insufficient hypothalamo-pituitary-gonadal axis in cryptorchid infants. Neither testosterone biosynthesis disorders nor enzyme inhibitions were found.

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GERM CELL NEOPLASIA IN PATIENTS WITH ABNORMAL SEXUAL DIFFERENTIATION

In 7 patients, aged 7 to 19 years, germ cell neoplasia was seen in their dysgenetic gonads. Four had male pseudohermaphroditism with 46 XY karyotypes, bilateral testes, ambiguous genitalia and persistent mullerian structures. Two had 46 XY pure gonadal dysgenesis and one was a 46 XX true hermaphrodite with bilateral ovo-testes. The gonads were intra-abdominal or inguinal. The most common tumour was a gonadoblastoma, present in 6 patients, bilaterally in 4 and oestrogen-secreting in 1. Malignancy was seen in tissue adjacent to the gonadoblastoma in 4 of the patients in the form of carcinoma-in-situ in the seminiferous tubules in 2, seminoma in 1 and yolk sac tumour with trophoblastic differentiation in 1. In one of the patients with pure gonadal dysgenesis only dysgerminoma was seen. Five variants of germ cell neoplasia were therefore present in these patients who appear to be at high risk of malignancy even during the pre-pubertal period. This reinforces the indication for early gonadectomy in XY gonadal dysgenesis and removal of intra-abdominal testicular tissue in true hermaphroditism.

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VULNERABILITY OF THE HUMAN LEYDIG CELL TO RADIATION DAMAGE IS AGE-DEPENDENT.

Testicular function has been studied in 3 groups of patients previously treated for malignant disease. Group 1 consisted of 14 men treated by unilateral orchidectomy only for a testicular teratoma (19-52 years). Group 2 consisted of 30 men treated for a testicular seminoma by unilateral orchidectomy and post-operative radiotherapy to the remaining testis (3000 cGy over 27-28 days)(21-54 years). There were 5 young men (age 14-34 years) in group 3, all of whom had been treated for testicular or pelvic tumours by unilateral orchidectomy and post-operative radiotherapy (3000 cGy over 26-35 days) between the ages of 1-4 years.

In group 2, 3 years post-irradiation, the mean basal FSH (29.3 IU/L) and LH (17.7 IU/L) concentrations were significantly greater and mean basal testosterone level (13 nmol/l) significantly lower than in group 1 ($p < 0.01$). All 5 males in group 3 showed grossly elevated basal FSH (> 32 IU/L) and LH (> 32 IU/L) concentrations with a mean basal testosterone level (1.8 nmol/l) significantly lower than in groups 1 and 2 ($p < 0.01$). None of the five showed a testosterone response to an HCG stimulation test or underwent puberty spontaneously.

CONCLUSION The severe reduction in testosterone levels in group 3, compared to group 2, despite the similarity of radiation dose received, suggests a much greater vulnerability to radiation-induced leydig cell damage in the prepubertal boy compared with the adult male.

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DNA ANALYSIS OF XX MALES WITH GENITAL ABNORMALITIES COMPARED TO "CLASSICAL" XX MALES.

5 male patients with a 46,XX karyotype were studied at both the DNA level to check for the presence of Y chromosome sequences and at the hormonal level for FSH,LH and testosterone (T).Patients were A 13 years old, B 151/2 years old, C 16 years old, D 21 years old and E 23 years old. Patients A, D, E had vaginal pouch, bilateral cryptorchism and hypospadia. Gonadal biopsy analysis showed that all 3 patients had testis. Patients B and C had normal genitalia with small testis. The hormonal data are as follows :

	A	B	C	D	E
T ng/ml	1,6	7	1,8	0,7	10,3
LH mUI/ml	13	5,8	5,8	17,5	9,4
FSH mUI/ml	23	18	18	20	14

The T levels are variable and non linked to the phenotype. LH levels are not feed-back inhibited by T.

Southern blot analysis of the 5 patients using Y specific DNA probe failed to detect Y DNA sequences in patients A, D, E. Y DNA is present in the genome of the others. These data suggest a heterogeneity in the XX male syndrome since we can distinguish two kinds of XX males : those with Y DNA material and those without detectable Y sequences yet displaying abnormalities in their genitalia.

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SERUM LEVELS OF FIBROBLAST GROWTH FACTOR IN CHILDHOOD AND ADOLESCENCE : A PRELIMINARY STUDY

Basic Fibroblast growth factor (FGF) is a polypeptide of 17.000 PM, isolated from various bovine and human tissues. This factor has a strong mitogenic activity and maintains differenciation of mesodermic cells in vitro, but its physiological role remains unknown. We used a radioimmunoassay (RIA) developped by Guillemin et al, Using antibodies raised against a synthetic replicate of |Tyr10| FGF (1-10). Our RIA intraassay and interassay coefficients of variation were 14% and 7% respectively. 83 children, 44 boys and 39 girls aged from 1 year 1 month to 15 years 10 months ($\bar{m}$: 6 years 6 months) were studied. FGF mean value was 20,01 $\pm$ 6,18 pmol|ml. A great disparity of individual values was found. No significative difference was found between boys (18,76 $\pm$ 6,28 pmol/ml) and girls (20,87 $\pm$ 5,84 pmol/ml). FGF values did not correlated with chronological age, but analysis of the results showed a slightly increase of FGF values with a maximum peak in prepubertal stage (10-12 years) followed by a slow decrease in pubertal children (12-16 years). We had previously studied 135 adults men and women. Adult FGF levels were lower than in children ($\bar{m}$: 18,34 $\pm$ 4,44 pmol/ml, $p < 0,05$) and no sex difference was found. Mean FGF value in blood cord of 8 neonates boys was lower than in 146 years children ($\bar{m}$: 15,58 $\pm$ 3,83 pmol/ml, $p < 0,05$). This preliminary study suggests that seric FGF determination could be a way to investigate the role of FGF in vivo and particularly in growth and development.