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Determination of serum somatomedin levels in patients with Cushing's syndrome by competitive protein-binding assay.

A competitive protein-binding assay has been developed using: 1) a rat liver protein which proved specifically to bind somatomedins (SM) and 2) ^{125}I NSILA-S* as tracer and NSILA-S*(4.5mU/mg) as standard. NSILA-S, SM-A** and serum SM extracted by acidic gel filtration gave parallel displacement curves. Results are expressed in relation to a standard pool of serum from normal adult males arbitrarly assigned a value of 1 U/ml SM.

11 adults and 7 children with Cushing's syndrome were studied. In *untreated patients*, the mean ± SEM levels (0.85 ± 0.07 U/ml, n=15)were not significantly different from those of normal adults (1.07±0.1,n=9). The cortisol levels were 20.9±2.7 µg/100ml (normal 10 ± 0.5). In the 7 children whose mean growth rate was 1.4 cm/year, SM levels (0.86±0.12 U/ml) were significantly higher ($p < 0.001$) than those in 8 hypopituitary dwarfs of the same age (0.21±0.05). In 10 *treated patients*, the mean SM levels were 1.04±0.11 U/ml and the cortisol levels 4.7 ± 1.6 µg/ml.

In 6 untreated patients, SM activity was determined by the chick embryo assay. Mean levels (0.72±0.06 U/ml) were below normal ($p \sim 0.05$). The results would suggest that the growth arrest in Cushing's syndrome is not a consequence of impaired SM synthesis.

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The effect of the sulfonylurea glibenclamide on different growth parameters in hypophysectomized male rats.

Evidence has been presented that insulin may be a growth promoting hormone. Therefore 26 male rats, bodyweight 60g, were hypophysectomized and injected i.p. for 10 days with saline (A) or 1 mg/kg/day glibenclamide (B). 24 hours after the last injection body weight, serum insulin=IRI, serum somatomedin=SM (porcine cartilage assay), and the epiphyseal plate of the proximal tibia (Greenspan assay) were measured. After 10 days the weight gain was not different, while treatment had increased: IRI(A) 4.9 ± 2.9*µU/ml vs (B) 8.0 ± 0.9 µU/ml, $p < 0.01$; SM(A) 0.41 ± 0.05U/ml vs (B) 1.06 ± 0.34 U/ml, $p < 0.001$, and the epiphyseal plate of the proximal tibia: (A) 181 ± 22.6 µm vs (B) 204 ± 17.4 µm, $p < 0.005$. The results show that glibenclamide stimulates growth, probably by increasing IRI, which may stimulate growth directly or indirectly via SM generation. Alternatively the sulfonylurea may directly augment SM. *M ± S.D.

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Somatomedin, growth hormone and growth velocity : relationships with transferrin.

Transferrin (Tf), somatomedin activity (SM), growth hormone (GH) and growth velocity (GV) were studied in 54 children.

Controls with constitutional variations of height within the normal range were given ornithine infusion: the induced rise of GH correlated with a simultaneous fall of SM ($n = 23$, $r = 0.711$, $p < 0.001$) and with a fall of Tf occurring 15 min. earlier ($n = 17$, $r = 0.610$, $p < 0.01$).

In 17 obese children SM was in the normal range (1.08 ± 0.11 U/ml), basal Tf was higher (2.86 ± 0.07 mg/ml, $p < 0.01$) and GH after arginine was lower (4.46 ng/ml, $p < 0.001$) than in controls. Tf and peak of GH were negatively correlated ($r = -0.608$, $p < 0.01$).

In 14 hypopituitary children, 6 mg of hGH did not induced variations of Tf over 24 hours.

Tf was positively correlated to GV in controls ($n = 15$, $r = 0.704$, $p < 0.01$), the same correlation was found when adding obese and hypopituitary subjects to the control group ($n = 41$, $r = 0.698$, $p < 0.001$).

The whole of these data suggest that Tf is involved in growth regulation and related to GH secretion by a feedback mechanism.

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Testosterone therapy in boys with tall stature.

Eleven tall boys were treated with testosterone using a long acting testosterone preparation in a mean dosage of 532 ± 147 mg/m²/mo. Treatment was considered justified if predicted adult height was 195 cm or more. Mean duration of treatment was 2,1 years. Chronological age at start of treatment ranged from 8,5 to 16,1 years ($\bar{x}$=12,62 ± 2,39), bone age ranged from 11,1 to 15,7 acc. to the TW II (RUS) method. Parent's height was $\bar{x}$=188,7 ± 8,52 for the fathers, and 175,1 ± 6,43 for the mothers. Mean predicted adult height was acc. to Bayley-Pinneau 205,17 ± 12,02 cm and 206,92 ± 13,03 cm acc. to Tanner. All boys except two were in puberty when treatment was started and adults at the time of evaluation. On the basis of bone age (RUS TW II) at start of treatment, 3 groups were formed: group I: 3 boys with a bone age of < 12 years ($\bar{x}$=11,25), group II: 4 boys with a bone age of 12-14 years ($\bar{x}$=13,27), group III: 4 boys with a bone age of > 14 years ($\bar{x}$=15,0). Mean height reduction amounted to 11,4 ± 6,9 cm for all boys together. Group I: 20,5 ± 3,0 cm; group II: 8,5±4,1 cm and group III: 5,3±1,5 cm. Hence it follows that the reduction is the greater the earlier therapy is started. Side effects were in general of minor degree. In 2 boys we had to discontinue the treatment (severe akne and psychic disturbances).

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The sequence of changes in testicular responsiveness to HCG stimulation and FSH priming in rats during sexual maturation.

Testicular responsiveness to HCG alone and with FSH priming in intact rats of 26,35,45,56,65 and 76 days of age has been systematically investigated. Circulating levels of testosterone and its two potent androgenic metabolites, 5α-dihydrotestosterone(DHT) and 3α,5α-androstanediol(Adiol)before and after various doses of HCG (10,20 and 40 IU per 100 g b.w.) were taken as the index of testicular responsiveness and measured by radioimmunoassay. The effects of FSH priming before HCG administration were also studied. Testicular responsiveness to HCG progressively increased during maturation recording maximum (average 4600% of the basal values) at age 35 and 45 days. 20 IU of HCG per 100 g b.w. was enough to provoke maximum stimulation which was indistinguishable from that due to a larger dose. DHT and Adiol were maximally stimulated with HCG at 45 days showing no further increment with maturity. The magnitude of the response for DHT and Adiol appeared to be neither related to the dose of HCG nor to the pretreatment with FSH. This study postulates that changing androgen response to HCG may be a major factor in sexual maturation in the male rat and it is influenced by the FSH pretreatment only in the mature animals.

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Reproductive Capacity and Ultrastructure of Testis after LH-RH or HCG Therapy for Cryptorchidism.

13 biopsies (A) from cryptorchid boys treated previously with LH-RH nasal spray were obtained during orchidopexy. For comparison 14 biopsies (B) from cryptorchid boys unsucessfully treated with HCG and 10 biopsies (C) without treatment were also obtained during surgery and examined by light and electromicroscopy. All boys were of the same chronological age: A (2.9 ± 1.8), B (2.6 ± 0.9) and C (3.0 ± 1.5) years old. The normal descendent testicle has 1.4 ± 0.3 spermatogonia per tubulus while cryptorchid boys had significantly lower spermatogonia tubulus (A - 0.38 ± 0.5; B - 0.43 ± 0.7; C - 0.35 ± 0.5). There was no significant difference between the three groups concerning the number of spermatogonia. This observation shows that neither HCG-therapy (5000 EI for 5 weeks) nor LH-RH-therapy (1.2 mg/day for 4 weeks) have a stimulatory effect on germ cells. The results also demonstrate that there are no anti-fertility effects of LH-RH therapy. The most striking feature of Leydig cells after LH-RH treatment is the marked increase of cell size and smooth endoplasmic reticulum. These changes were identical to those observed after HCG treatment. Ultrastructurally, the Leydig cells show signs of stimulation and increased secretory activity following LH-RH or HCG treatment for cryptorchidism.