● 481 A NEW TYPE OF LIGAND-INDEPENDENT PARTIAL ANDROGEN RESISTANCE DETECTED WITH THE AID OF THE SYNTHETIC ANDROGEN, 17α-METHYL MIBOLERONE (MB).

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Mutations that cause androgen resistance by altering various properties of the androgen receptor other than its maximum binding capacity (B_{max}) are termed receptor-positive (R^+). We have studied intact pubic and genital skin fibroblasts (SF) from an XY infant with markedly ambiguous genitalia. Their androgen receptor activity had a B_{max} of 20 fmol/mg protein (normal: 10-40), an equilibrium binding constant (K_d) of 0.7 nM (normal: ∿ 0.1), and failed to «up-regulate» in response to prolonged incubation with ∿ 3 nM MB (normal: 2- to 4-fold during 72 h). In addition, the mutant MB-receptor complexes dissociated with a half-life of 52 min at 33°C (normal: 300), and were more thermolabile than normal (<10% remained after 4 h at 42°C; normal: >50%). In contrast, the unliganded mutant receptor activity had a normal half-life (at 37°C, 10 h; at 42°C, 80 min). The aberrant properties were also demonstrable with 5α-dihydrotestosterone, or with a second synthetic ligand, methyltrienolone. Conclusions: (i) these data reveal a severely defective R^+ mutant androgen receptor that is distinct from any we have described heretofore (J Clin Endocrinol Metab 59: 679, 1984); (ii) the native mutant receptor does not misbehave until it is, or has been, bound to ligand; (iii) the latter suggests that free receptor molecules derived from mutant MB-receptor complexes differ from their never-liganded counterparts.

482 TRANSIENT GROWTH DECELERATION IN NORMAL SHORT CHILDREN.

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Several studies have been reported, in which children with growth retardation have been used as their own growth velocity (GV) controls in evaluating therapeutic interventions. In order to judge the validity of such an approach, the natural history of GV before and after a timepoint at which child is likely to be enrolled in such a study must be known.

We have examined the GV of 24 children who underwent growth hormone (GH) testing because of concern about their growth (Height <3d centile, GV <5cm/yr), but were found not to be GH deficient. They were 17 boys and 8 girls, ranging in age from 2 to 16 yrs. (mean 10.05). Mean GV before testing was 3.8 cm/yr. Following testing, and without any specific treatment, GV was greater in all but 2 of them, with a mean of 5.1cm/yr. The difference (mean±SEM) was 1.3±0.298, p=0.0016) Thus, a transient growth deceleration appears to occur in some non- GH-deficient children, during which they are most likely to be referred for testing and subsequently be enrolled in a therapeutic trial. This creates an ascertainment bias that may produce spurious evidence of effectiveness of the intervention under evaluation. Matched or randomized controls are essential in such studies.

483 PITUITARY FUNCTION IN PRIMARY MALNUTRITION DUE TO ANOREXIA NERVOSA AND OTHER EATING DISORDERS.

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The effects of nutritional state on pituitary function were studied using a combined pituitary stimulation test in 3 groups of 10 patients each. 1-Classical Anorexia Nervosa (AN) with a weight deficit for height (WDH) of 26.0±8.1%, aged 12-19 years. 2-Non-AN eating disorders with a WDH of 12.5±8.6%, aged 12-17 years. 3-Familial or constitutional short stature without pathological WDH and no nutritionally based growth disorder, aged 10-16 years. Each patient received seqentially IV TRH, LRH, regular insulin and PO L-Dopa. Serum TSH, glucose, cortisol, GH, LH and FSH, and prolactin were sampled periodically over 2 hrs. Basal T_3, T_4, Somatomedin-C and other chemistries were obtained. The peak TSH response was blunted and delayed in direct relation to the WDH. The ratio of the integrated TSH response from 0 min. to 45 min. divided by the 45 min. to 120 min. response was correlated to the WDH ($p<0.001$) and to recovery from hypoglycemia ($p<0.001$). Also, the recovery from hypoglycemia ($p<0.001$), the basal cortisol ($p<0.05$), and transferrin ($p<0.05$), all correlated to the WDH. The transferrin correlated to the T_3 ($p<0.01$). The most underweight patients had the lowest T_3, basal glucose and Somatomedin-C levels. This study shows the newly described integrated TSH ratio to correlate well to the WDH and the ability to recover from stress. Also demonstrated was that the responses noted were independant of the etiology of the eating disorder which resulted in the malnourished state.

● 484 HYPOPITUITARISM IN CHILDREN WITH "PRIMARY EMPTY SELLA SYNDROME (PESS)",

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78 children with retardation of growth and/or sexual maturation had pituitary dynamic studies, nocturnal growth hormone (GH) sampling and CT scan for suspected GH deficiency. In 19/78, PESS was diagnosed by high resolution CT scanning (5 girls and 14 boys). Bone age was delayed, but sella turcica was normal in size and shape in all PESS patients. Ten of the patients had normal pituitary studies. Two of the patients (I & II) had panhypopituitarism (GH, TSH & ACTH deficiencies). In 4 patients (III-VI), peak GH was <7.0 ng/ml. In 3 others (VII-IX), peak GH was 8.1-9.8 ng/ml. One patient (I) remained hyperprolactinemic even after thyroid replacement.

Patient	T4	TSH	Max GH	Cortisol		Prolactin
	µg/dl	µu/ml	ng/ml	Basal (µg/dl)	Peak	ng/ml
I	5.2	5.2	2.6	6.0	12.0	51.0
II	5.0	7.2	1.5	1.0	9.4	--
III	9.3	1.3	3.2	10.5	24.5	16.3
IV	11.8	4.1	4.4	6.1	24.3	8.9
V	8.1	2.0	3.2	14.4	17.6	5.9
VI	10.3	2.6	6.6	11.2	22.2	13.4
VII	7.9	2.9	8.1	10.5	37.4	--
VIII	10.4	1.6	9.8	10.1	14.7	--
IX	8.4	2.2	9.7	9.3	22.1	16.3

Conclusions: 1. PESS is not uncommon in growth retarded children; 2. It may be the cause of "idiopathic hypopituitarism".

485 ROLE OF SOMATOMEDIN-C (SMC) IN LYMPHOCYTE PROLIFERATION.

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As lymphocytes have receptors for SMC, we studied the role of SMC in lymphocyte proliferation. Peripheral lymphocytes from 27 controls and 17 children with growth hormone deficiency (GHD) were cultured in either autologous serum (AS) or pooled serum from normal adults (NS) with and without phytohemagglutinin(PHA). The mitogenic response (MR) was defined as thymidine incorporated in AS÷thymidine incorporated in NS. Control MR = 1.01 ± 0.05 (X ± SEM). Two different MRs were observed in the untreated GHD children. Most GHD sera had a normal MR (1.09 ± 0.06), but 4 had a very low MR (0.05 ± 0.02). MR did not correlate with SMC or growth rate. The two groups of children were similar in all other parameters that we measured. After 1 week of growth hormone treatment (0.1U/kg/d), MR was normal in all (0.97 ± 0.06). Partially purified SMC (10-500 ng/ml) did not increase MR in the presence of varying (0-5%) amounts of AS. Although PHA stimulated lymphocyte proliferation, culture medium SMC was not increased and was proportional to the SMC content of the serum used ($r = 0.8$). Conclusions: SMC does not have a direct role in lymphocyte proliferation since the MR in GHD serum was not proportional to SMC; exogenous SMC did not increase MR nor was SMC synthesized by lymphocytes in vitro. Serum from some GHD children lacks another factor(s) that supports lymphocyte proliferation in vitro.

486 DEMONSTRATION OF 2 POOLS OF GONADOTROPINS IN PERIPUBERTAL CHILDREN BY A 2 PHASE LHRH TEST.

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We investigated whether puberty might be characterized by the ability to secrete gonadotropins (Gn) in response to LHRH infusion after the readily releasable pool of Gn is exhausted. We studied 14 girls and 16 boys ages (CA) 6 to 19 and bone ages (BA) 8 to 14. A 100 µg bolus (B) of LHRH was followed 1 hour later by an infusion (I) of 100 µg LHRH over 2 hours. 6 girls with precocious puberty and 7 boys with delayed puberty had responses indistinguishable from controls (p>.05, see table). 3 boys and 1 girl, CA 16-19, BA 13.5 to 15 with Gn deficiency had an area under the curve that was clearly different from controls. In all subjects a comparable amount of gonadotropin was secreted during I as following B (r=>.95, p<.001 for both LH and FSH).

Mean value for	Δ LH		area LH		FSH		area FSH	
	B	I	B	I	B	I	B	I
control ♀ /7	24.2	42.0	1375	2285	19.2	38.8	1341	2201
prec pub ♀ /6	29.1	44.6	1584	2352	32.0	98.5	1796	3857
control ♂ /6	12.7	12.1	811	930	10.9	18.0	719	1437
delay pub ♂/7	22.3	26.8	1320	1565	4.8	9.5	546	869
Gn deficiency/4	2.0	1.3	239	222	2.3	2.3	228	226

We conclude from these data that (1) the slowly releasable gonadotropin pool is as large as the readily releasable gonadotropin pool in both clinically prepubertal and pubertal subjects; (2) for most diagnostic purposes an infusion of LHRH has no advantage over bolus administration.