● 437 HUMAN GROWTH HORMONE (HGH) DEFICIENCY AND POLYMORPHISM WITHIN THE HGH AND HUMAN PLACENTAL LACTOGEN (HPL) GENE CLUSTER

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Restriction mapping discloses polymorphism of base sequences within the HGH/HPL gene cluster on human chromosome 17. Cellular DNA specimens from 30 normal, unrelated subjects were digested with the enzymes Eco RI, Bam HI and Bgl II and hybridized to ^{32}P HPL cDNA. The following band patterns were observed:

Enzyme	Standard Fragment Sizes (kb)	Variant Forms	#/30
Eco RI	8.6 7.2 6.2 2.8=HPL 2.5=HGH	Extra 3.4	6
Bam HI	7.7 7.3 6.6 5.5 3.8 2.9 0.8 0.5	Minus 7.3	6
Bgl II	9.4 8.6 7.5 7.2 3.0 2.0 1.9 1.7	Minus 3.0	2

To determine relationships between HGH/HPL gene variation and hormone deficiency, patterns were examined for 6 children with nonfamilial HGH deficiency and 2 pairs of siblings with autosomal recessive, partial HGH deficiency. No unique HGH/HPL restriction patterns were found. Further, one pair of affected siblings was discordant for loss of the 7.3 kb Bam HI band and the other pair was discordant for loss of the 3.0 kb Bgl II band. This indicates that the mutation responsible for their disorder is not linked to the HGH/HPL gene cluster on chromosome 17.

438 EXCRETION PATTERNS OF 6-HYDROXYMELATONIN IN PUBERTAL AND PREPUBERTAL CHILDREN.

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Pineal secretion of melatonin is hypothesized to suppress gonadal development in both experimental animals and man. A recent report by Silman et al demonstrated a marked decrease in blood melatonin in males but not in females at the time of the onset of puberty.

We have developed a gas chromatographic-mass spectrometric method for urinary 6-hydroxymelatonin, which is the major metabolite of melatonin excreted by man. We have previously shown that normal adults exhibit a circadian pattern for urinary excretion of 6-hydroxymelatonin with a total excretion ranging to 6-18 µg/24 hrs and with greater than 80% of the total excretion being from 12 midnight to noon. The urinary excretion of 6-hydroxymelatonin appears to reflect the pineal secretion of melatonin.

We measured the circadian excretion of 6-hydroxymelatonin in 24 normal children ages 3-15 years to determine whether the pattern or amount of 6-hydroxymelatonin excreted varies with age and pubertal development and specifically whether a decrease in excretion might accompany the onset of puberty. The normal children showed the same circadian rhythm as adults with the range of total secretion of 8 to 20 µg/24 hours.

Our data suggests that the pineal gland in children secretes adult levels of melatonin beginning at the earliest ages studied.

● 439 ACUTE AND CHRONIC USE OF THE ANGIOTENSIN I CONVERTING ENZYME INHIBITOR (CAPTOPRIL) IN CHILDHOOD HYPERTENSION.

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Three patients, aged 10-18 yrs, with uncontrolled hypertension, have been treated with the angiotensin I converting enzyme inhibitor (captopril) for 15-29 mos. Their diagnoses are malignant hypertension of unknown etiology, Takayasu's arteritis with renal involvement and single kidney hydronephrosis and renal artery stenosis. Two patients had four test doses of oral captopril in doses of 12.5-50 mg. The changes in Mean Arterial Pressure (MAP) and Plasma Renin Activity (PRA) at 90' were:

MAP(mm Hg)	Average	Range	PRA(ng/ml/hr)	Average	Range
Pre	142	132-155		12.9	6.1- 23
Post	120	105-133		61.5	28-110
Change %	↓15.6	↓5.3-25		↑376	↑243-587

Serum aldosterone decreased by 90' in all tests by an average of 81.2%, range 78.1-91.2%. The MAP in two patients on captopril alone, 150-250 mg/day, decreased by 6.4 and 18.8%. The third, with Takayasu's arteritis, is taking prazosin in addition to 400 mg of captopril. His MAP has decreased by 9.6% but he remains severely hypertensive. In all three PRA has remained elevated and serum and urinary aldosterone levels have remained suppressed. Retinal and cardiac hypertensive changes have improved. We conclude captopril can be a useful therapeutic modality in the treatment of uncontrolled childhood hypertension.

440 SERUM DEHYDROEPIANDROSTERONE SULFATE (DHEAS) AS A PREDICTOR OF PUBERTY IN CHILDREN WITH HYPOPITUITARISM.

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Evaluation of gonadotropin secretion in prepubertal children with hypopituitarism yields little information and it is often impossible to predict whether a patient will undergo pubertal changes. In normal children, an increase in serum levels of DHEAS precedes pubertal development by several years. Whether this hormone plays any role in the pubertal process of children with hypopituitarism remains unclear. We have measured serum levels of DHEAS sequentially (prospectively and retrospectively over a 7 year period) in 17 patients with hypopituitarism (idiopathic=12) who are currently over 15 years of age. The levels were compared to those obtained in 82 normal children (6 to 18 years of age). Patients could be divided into 2 distinct groups, one (11 patients) with very low or undetectable levels and a second group (6 patients) with normal levels of DHEAS for their bone age. None of the patients from group I entered puberty and all are now receiving replacement therapy. All patients from group II developed puberty spontaneously (Stages II to IV). Retrospectively, all patients in group II had had normal levels of DHEAS for their bone age and the levels had increased gradually with advancement of bone age. These data indicate that serum levels of DHEAS may be utilized to predict which children with hypopituitarism will undergo spontaneous puberty.

441 EFFECT OF HUMAN GROWTH HORMONE (hGH) ON PLASMA LEVELS OF EPINEPHRINE (E) AND NOREPINEPHRINE (NE) IN HYPOPITUITARY CHILDREN.

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Plasma levels of E and NE in response to insulin induced hypoglycemia were measured in 4 children (ages 7 to 14 years) with isolated hGH deficiency before initiation of hGH therapy and one month after treatment with hGH (2 U three times/week). Since plasma levels of E and NE are directly related to the degree of hypoglycemia, attempts were made to induce a similar degree of hypoglycemia before and after treatment with hGH (Table). Plasma levels of E and NE were measured by radioenzymatic assay. Although basal plasma levels of E and NE remained unchanged after hGH therapy, the response of plasma E to hypoglycemia was decreased in all patients after treatment (Table). The response of plasma NE was not affected by hGH therapy. These data indicate that basal plasma levels of E and NE are not affected by hGH while response of E to hypoglycemia is exaggerated in patients with hGH deficiency. This may be a compensatory mechanism for combating hypoglycemia in these patients. Treatment with hGH diminishes the need for E and normalizes the response. The reason for the wide range of plasma levels of E during hypoglycemia remains unclear.

	Blood Sugar	Basal (pg/ml)		Peak (pg/ml)	
Range	Nadir mg/dl	E	NE	E	NE
Before hGH	29-35	49-99	157-298	765-4226	383-857
During hGH	31-38	32-176	212-289	191-3671	260-847

● 442 BIOACTIVE LH PITUITARY RESERVES DURING NORMAL/ABNORMAL MALE PUBERTY.

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We explored the possibility that the serum bioactive LH (B-LH) response to gonadotropin releasing hormone (GnRH) infusion might provide additional insight into normal and abnormal pubertal maturation. Controls consisted of 24 boys and 10 men; 1 true isosexual precocity (TIP) and 11 hypopituitary (11-53 yr) cases were studied. Maturationa. staging was by AM testosterone (T). B-LH was assayed by rat leydig cell T production, immunoreactive LH (I-LH) by RIA.

Normally the GnRH-induced B-LH was related to maturational stage in a biphasic manner (cubic fit r=0.85): a) stimulated B-LH is minimal in the most immature children (rising only from 23 to 26 ng/ml in the youngest), b) undergoes an initial rise at T = 20-40 ng/dl ($p < .05$), c) peaks at a T level of 196 ng/dl, and d) then declines modestly ($p < .05$) as the T level rises further. B-LH was not so closely related to chronologic age, bone age, or Tanner stage. The pubertal peak in LH was not seen in I-LH data, but was in B-LH/I-LH (B/I), a measure of LH biopotency.

The TIP case had elevated basal B-LH, stimulated-B-LH, and B/I, though I-LH was normal. The abnormalities were progestin-suppressible.

Stimulated B-LH corresponded better than I-LH to the maturation achieved by hypogonadotropic men. B-LH responses to GnRH discriminated teenagers with delayed puberty from those with gonadotropin deficiency once T levels exceeded 30 ng/dl.

In summary, the normal biphasic relationship of B-LH reserve to the baseline T level is an improved diagnostic criterion for distinguishing hypogonadotropinism from delayed puberty.