HETEROGENEITY OF RESPONSE TO LH-RH IN PATIENTS WITH THE SYNDROME OF CONGENITAL ANOSMIA AND HYPOGONADISM. Alan Rogol and Saul Rosen, (intr. by Paul di Sant'Agnese), NIH, Bethesda, MD.

The syndrome of congenital anosmia and hypogonadism ("the Kallmann Syndrome") is part of the differential diagnosis of delayed pubescence in both sexes. To attempt to define the locus of the defect we studied the response of 12 patients (5F,7M) to luteinizing hormone releasing hormone (LH-RH). All patients initially presented with a history of delayed pubescence, had low levels of serum estradiol or testosterone and congenital anosmia, and were unable to detect pure exaltolide or floral. There was no evidence of pituitary tropic hormone deficiency except for gonadotropins.

Synthetic LH-RH (100μg, Ayerst) was administered as a single subcutaneous dose. "Release" was measured as the integral increase over the mean of 3 baseline samples of FSH and LH measured serially during a 6 hour period. Three types of response were observed. Two men showed trivial release (<720 mIU x min) for both LH and FSH. The majority (4M,5F) had release of 1100-8000 for LH and 600-2300 for FSH. One man with spermatogenesis and erythrocyte phenotype-compatible paternity, displayed enhanced LH release of 24,000 (with a basal LH of 38 and peak of 190) but basal FSH (<4), peak FSH (20) and FSH release (2000) were not different from the majority of responders.

These data are compatible with heterogeneity of response to LH-RH in the syndrome of congenital anosmia and hypogonadism.

EFFECT OF ANTI-BOVINE LUTEINIZING HORMONE(LH)AND ANTI-RAT PROLACTIN(PRL)SERA UPON THE SECRETION OF LH IN INTACT ADULT MALE RATS. Allen W.Root and Gregory E.Duckett. University of South Florida Col.of Med., All Children's Hosp.,Dept.of Pediatrics, St.Petersburg.

Antisera to bovine LH and rat PRL prepared in rabbits were administered s.c. to intact adult male rats daily for 10 days. Control animals received non-immune rabbit serum. Animals were sacrificed by decapitation without anesthesia 24 hrs.after the last injection. Serum and pituitary LH levels were determined by radioimmunoassay. LH data are expressed in terms of NIAMDD Rat LH-RP-1. Testicular and ventral prostate weights were significantly ($p<0.01$) reduced in animals who had received anti-bovine LH serum. There were no effects of anti-bovine LH serum upon body,pituitary or adrenal weights. Pituitary LH concentration was significantly higher in anti-bovine LH serum-treated animals than in control rats(31.2±6.5(SD) μg/mg pituitary vs 22.7±6.8 μg/mg, $p<0.02$). Serum LH levels were higher in animals who had received anti-bovine LH serum than in control rats. Anti-rat PRL serum had no significant effect upon body,pituitary,testicular,ventral prostate or adrenal weights or upon pituitary LH content or concentration. Serum LH concentrations in anti-rat PRL serum-treated animals were higher than in control animals. Inhibition of gonadotropin activity by anti-LH serum resulted in compensatory increase in LH secretion. Data suggest that anti-PRL serum may also interfere with hypothalamic-pituitary-testicular function.

EFFECTS OF PHYSIOLOGIC ESTRADIOL THERAPY ON NEUROENDOCRINE & SOMATIC MATURATION. R.L. Rosenfield and V.S. Fang, Univ. of Chgo. Pritzker Sch. of Med., Dept. Ped. & Med., Chicago, Ill.

Studies have been made of the effects of chronic, physiologic estradiol (E2) therapy on skeletal growth and evolution of mature hypothalamic-pituitary regulation of gonadotropin release, as well as sexual development. The response to 1-2 mg/month depot E2 im for 1-1 1/2 yrs was studied in 7 cases of Turner's syndrome and 1 with multiple endocrine deficiencies with average age 16 yrs., LH 278 and FSH 1582 ng/ml.

Doses of 1.5-2 mg E2 uniformly induced breast development and menarche. Sexual hair progressed in all patients, independently of the onset of adrenarche. The growth rate doubled to 1.4 in./yr. The average growth rate per year advancement of skeletal age was unchanged by E2 therapy.

Before therapy the height and suppressibility of the gonadotropin level were independent of age. When E2 was withheld after 1 yr therapy, LH and FSH were similar to before. However, subsequent E2 injection did not inhibit LH as much as before ($p< .01$), although depression of FSH was comparable.

Conclusions: 1) These studies indicate that physiologic doses of E2 do not deleteriously affect epiphyseal fusion and growth potential. Therefore, this appears to be an optimal therapeutic regimen. 2) These studies demonstrate for the first time that an early event in puberty is reduced sensitivity to E2 of the specific negative feedback mechanism controlling LH release. Furthermore, this change in the hypothalamic-pituitary axis seems to be induced by E2.

THE MECHANISMS OF NEONATAL THYROIDAL HYPERACTIVITY IN THE NEWBORN SHEEP. Joseph Sack, Mark A. Beaudry, Paul V. DeLamater, William Oh & Delbert A. Fisher, UCLA Sch. Med., Harbor Gen. Hosp., Dept. Ped., Torrance, California.

We have reported data in the human newborn suggesting that the early TSH surge and subsequent hyperthyroid state is due to extrauterine cooling. We now report further studies of this phenomenon in the newborn sheep. Uterotomies were performed on 8 pregnant ewes at term. Three lambs were delivered into room air (21-22° C), five were delivered into 40° C water bath and kept there for 60 min. with cord intact. They were then exposed to room air for an additional 60 min. Rectal and skin temperatures, pulse and blood pressure were monitored serially. T4 and T3 were determined in serum by RIA. Base line T4 values were similar in both groups and did not change significantly during the studies. Mean T3 levels, initially similar in both groups, increased 300% by 60 min. and 672% ($p < 0.01$) by 120 min. of exposure to room air; mean values in water bath fetuses did not change in or out of the bath. Three/3 exposed fetuses survived and 3/5 of the water bath fetuses died with hypothermia when exposed to room air. The data indicate that neonatal thyroidal hyperactivity is associated with extrauterine cooling but that other factors associated with initial extrauterine exposure must be involved. The T3 response may be important to survival.

A DOMINANT FORM OF ISOLATED GROWTH HORMONE (GH) DEFICIENCY ASSOCIATED WITH RIEGER'S SYNDROME (RS). A.Sadeghi-Nejad and B. Senior. Pediatric Endocrine-Metabolic Service, Tufts-New England Medical Center Hospitals, Boston.

The transmission of isolated GH deficiency as a recessive disorder is well documented. However, the evidence for transmission as an autosomal dominant is less secure. RS is a rare autosomal dominant disorder characterized by malformation of the iris, and dental and maxillary hypoplasia. A child with RS was short and lacked GH. His father and a sister also had RS and lacked GH. The paternal grandmother and paternal uncle had RS, were extremely short but refused investigation.

| GROWTH HORMONE (ng/ml) | | 0' | 15' | 30' | 60' | 90' |
|---|---|---|---|---|---|---|
| Propositus | Insulin stimulation | 3.0 | - | 3.0 | 3.4 | - |
| | Insulin stimulation | 0.7 | - | 1.1 | 0.7 | - |
| Sibling | Insulin stimulation | 0.8 | - | 0.5 | 0.7 | - |
| | Arginine stimulation(Premarin) | 2.8 | 1.1 | 0.8 | 1.0 | 0.8 |
| Father | Insulin stimulation | 2.1 | - | 2.5 | 3.2 | - |
| | Arginine stimulation(Premarin) | 0.9 | 0.9 | 0.9 | 1.4 | 1.0 |

Pituitary function was otherwise normal. With hGH the propositus grew 25.5 cm in 4.5 years (1.8 cm the year before).

The abnormalities of RS involve tissues of both mesodermal and ectodermal origin. However, control of their differentiation is thought to reside in the neural crest. Since the anterior pituitary is functionally dependent upon the hypothalamus, a neural crest structure, both RS and the GH deficiency may derive from a common embryologic defect with the abnormality transmitted as an autosomal dominant.

PSYCHOSOCIAL DWARFISM: NORMAL SOMATOMEDIN (SM) GENERATION. Paul H. Saenger, Lenore S. Levine, Maria I. New, Eckehart Wiedemann, Ernest Schwartz. Cornell Univ. Med. Coll., Dept. of Ped., New York City and Bronx VA Hosp.

Study of a psychosocial dwarf with initial GH deficiency reveals that the dwarfism was not due to caloric deficit nor inability to generate SM in response to GH release. We present data on a 7 yr. old boy with a severe form of psychosocial dwarfism (PSD), who began a period of marked catch-up growth 3 weeks after admission (growth velocity 3 cm/month). During the period of poor growth the mean caloric intake was 1595 cal/day, in the period of catch-up growth it was 1504 cal/day. Since the weight increased in the period of catch-up growth the caloric intake per kg bodyweight actually decreased. The maximum growth hormone response during combined L-DOPA-ITT rose from 5.9 ng/ml to 13.6 ng/ml in the phase of catch-up growth. Somatomedin which was in the hypopituitary range of 0.59 U/ml rose concomitantly to a normal value of 0.84 U/ml. With separation from his favorite nurse his growth velocity dropped while in the hospital to 0.4 cm/month accompanied by an inadequate growth hormone release upon stimulation (max. GH 6.9 ng/ml). The caloric intake remained unchanged. With the return of his favorite nurse he resumed his previous growth velocity of 3 cm/month and stimulable growth hormone rose to 15 ng/ml. We conclude that growth failure in PSD is not due to caloric undernutrition but to defective GH release and inadequate SM generation which corrected with removal from the family milieu.