407 ORAL CLONIDINE AS A TEST FOR GROWTH HORMONE RELEASE IN SHORT STATURE (SS) AND TOURETTE'S SYNDROME (TS). J.Gertner, T.Lowe, M.Genel, G.Young and D.Cohen, Dept. Ped. & Child Study Center, Yale U. Sch. Med., New Haven, CT

The administration of C, an α_2 adrenergic agonist, induces GH secretion, sedation and hypotension. To test the hypothesis that these effects are independent of one another, we measured GH responses to oral C (4 µg/kg) in 14 SS patients whose post-exercise GH was <7 ng/ml and in 5 TS patients. Plasma C levels, blood pressure and degree of sedation were recorded as were plasma levels of 3-methoxy-4 hydroxyphenyl glycol (MHPG). To determine the persistence of GH responsiveness the 5 TS were re-studied after 3 mos Rx with C.

GH peaks (mean 17.4±3 ng/ml) occurred at 60-90 min. in all TS and 9/14 SS patients. There was no tendency for responsiveness to diminish after Rx with C with mean post Rx GH peaks of 22±5 ng/ml in the 5 TS. In 5/14 SS, all GH deficient on insulin testing, peak GH was <3 ng/ml. C levels rose to a peak of 1.2±3 ng/ml at 60', preceding the GH peak by 30'. An observed 12% fall in MHPG levels (attributable to a C-mediated reduction in central nervous system (CNS) noradrenergic activity) was not related to the timing or extent of the GH peaks. These peaks also bore little temporal relationship to the slight hypotension or marked sedation occurring after oral C. We conclude that C is a highly effective tool for the diagnosis of GH deficiency and that the GH response to C is sustained during chronic Rx with C. Our data support animal studies which suggest that C exerts its various effects at multiple sites in the CNS.

410 EVIDENCE FOR TONIC GAMMA-AMINOBUTYRIC ACID (GABA) MEDIATED INHIBITION OF GROWTH HORMONE (GH) SECRETION IN THE OVINE FETUS. Peter D. Gluckman (sponsored by M.M.Grumbach),Dept of Paediatrics,University of Auckland, Auckland, New Zealand.

Circulating GH concentrations are high in the fetus and fall after birth. The high fetal GH levels have been postulated to reflect immaturity of hypothalamic control of GH secretion. GABA mediated regulation of GH release was studied in chronically catheterized ovine fetuses (term 147 days) and infant lambs. Muscimol (MUSC),a GABA agonist (300ug/kg) was given iv to 3 fetuses (108-137 days) and GH fell from 123.6 ± 53ng/ml to 64.7 ± 25.7ng/ml ($p < 0.05$). In 2 younger fetuses (95,99days) no suppression was noted. Picrotoxin,(PIC),a GABA antagonist (500ug/kg) was given iv to 7 fetuses (80 - 140 days). Plasma GH rose from 76.3 ± 15.6ng/ml to 115.0 ± 8.5 ng/ml ($p < 0.05$). The incremental GH response to PIC rose with gestational age ($r=0.80$, $p < 0.05$). In 3 neonates, GH rose following PIC from 10.6 ± 8.5 ng/ml to 45.0 ± 13.9 ng/ml. Pretreatment with MUSC reduced the neonatal response to PIC (n=3) indicating that the action of PIC is mediated by GABA receptors. These data are evidence for GABA receptors in the fetal hypothalamic-pituitary unit. The GH response to PIC is evidence for tonic GABA mediated inhibition of fetal GH release in the late gestation fetus and neonate. This suggests that the high fetal GH levels do not represent entirely unrestrained activity of the hypothalamic-pituitary unit but that there is partial restraint of GH release mediated by GABA.

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● **408** CONTINUOUS SUBCUTANEOUS INFUSION OF GROWTH HORMONE (CSIGH) IN GROWTH HORMONE DEFICIENCY:FEASIBILITY AND SHORT TERM METABOLIC EFFECTS. J.Gertner, S.Page and W.Tamborlane, Dept. Ped., Yale U. School Med., New Haven, CT

In contrast to the sustained acceleration of growth observed in pituitary hypersecretion of GH, full catch-up growth is rarely attained in GH deficiency with conventional GH Rx (0.1 U/kg IM 3x/wk). Since circulating GH levels are very low for all but 24-30 hr per wk during conventional Rx, we examined the feasibility and short term metabolic effects of CSIGH using a small infusion pump. Fasting levels of glucose (G), insulin (I), free fatty acids (FFA) and oral glucose tolerance were determined in 5 previously untreated deficient children before and after 85 hrs of CSIGH (dose 2.1 µU/kg/hr ∿ 0.3 U/kg/wk).

CSIGH maintained serum GH levels at 3-9 ng/ml during the infusion. As shown in the table, CSIGH produced a modest increase in fasting (0 min) G and I. Furthermore, glucose tolerance was impaired despite 2-fold higher I levels (*$p<0.05$).

Plasma G:	0 min	60 min	90 min	I:	0 min	60 min	90 min
Pre-CSIGH	82±9	123±11	105±9		15±4	65±11	64±6
Post-CSIGH	97±10	153±11*	143±16*		27±6	133±23*	139±27*

FFA rose sharply after 12 hr CSIGH (1021±151 vs 605±87 µM, $p=0.05$) but later returned to baseline values. CSIGH was well tolerated by all patients. Conclusions: CSIGH in standard doses produces sustained increases in GH levels sufficient to alter lipid and carbohydrate metabolism and induce hyperinsulinemia. CSIGH might be an effective alternate approach to GH replacement therapy.

411 IDENTIFYING THE ACADEMIC AND EMOTIONAL DIFFICULTIES ASSOCIATED WITH SHORT STATURE. Michael Gordon, Carol Crouthamel, Ernest M. Post and Robert A. Richman (Spon. by Frank A. Oski). SUNY Upstate Medical Center, Departments of Pediatrics and Psychiatry, Syracuse, New York.

To determine if children with growth retardation are at greater risk for academic and emotional problems than those of normal stature, we studied twenty-five children of normal intelligence with constitutional short stature or growth hormone deficiency. On the Child Behavior Checklist, 44% of these children scored in the 90th percentile or higher on the overall index of behavioral difficulty, a level typical of children referred for mental health services. Our patients had specific elevations on indices of somatic complaints, schizoidal tendencies, obsessive-compulsive traits and depression. They also had a disproportionate incidence of excessive clowning (45%), being teased (65%), unhappiness (48%), and underachievement (41%). Another striking finding was that the children had a high prevalence of grade retention, 28% having repeated at least one grade, in spite of having normal intelligence (mean full scale IQ=105.3, S.D. 14.9). Furthermore, 30% of the subjects had a verbal IQ that was 20 or more points higher than the performance score, a discrepancy occurring in only 10% of the population. In conclusion, short children seem to be at increased risk for developing academic and emotional difficulties. To better define the development problems unique to these children, we are now administering an extensive battery of intelligence, achievement, and personality tests to our patients and a control group matched for age, sex and socioeconomic class.

● **409** CAN MENTAL RETARDATION BE COMPLETELY OVERCOME IN CONGENITAL HYPOTHYROIDISM? J. Glorieux, J. Letarte, J.H. Dussault, H. Guyda, J.Morissette. Departments of Pediatrics, Univ. of Montreal and McGill Univ., Montreal, and Department of Medicine, Laval Univ., Quebec, Canada.

Congenital hypothyroidism hampers the normal growth of body and mind. Initiation of therapy during the first 3 months of life is the most critical aspect in this disease. This finding has been decisive in the establishment of screening programs for neonatal hypothyroidism. Since 1974, the Quebec Network for Genetic Medicine has detected over 130 such cases. Their mental development has been assessed at 12, 18, and 36 months. The Griffiths Mental Scales of Development were selected as the best clinical indices for developmental evaluation because their 5 different scales are equally weighted at each age level. Comparison between hypothyroid children and controls has produced the following results. At 12 months: Hypos do not differ from controls. However, mean DQ for both groups is systematically above theoretical mean of 100 (114 and 113). At 18 months: Hypos gave lower results than controls in all scales, namely: locomotion, personal and social development, hand-eye coordination, hearing and speech, and performance. The results in the last two scales as well as for the total DQ were statistically different ($p < 0.01$). At 36 months: The patients maintained the same profile noted at 18 months. CONCLUSION: While the intellectual performance of hypothyroid babies is greatly improved by early treatment in life, this does not produce a totally normal mental development. This situation is already apparent at 18 months.

412 THYROID REGULATION OF PHOSPHOENOLPYRUVATE CARBOXYKINASE IN THE PERINATAL PERIOD OF THE RAT. Peter Hahn, Departments of Paediatrics, Obstetrics & Gynecology, University of British Columbia, Vancouver, B.C., Canada.

Triiodothyronine (T_3) is known to induce gluconeogenesis in the liver of adult rats. Hence we enquired whether it could be involved in the steep rise of phosphoenolpyruvate carboxykinase (PEPcK) activity described for the newborn. Two injections of T_3 (20 µg/100 g body weight each) to the mother rat on days 20 and 21 of pregnancy resulted in a ten to 50-fold rise in PEPcK activity in fetal liver. At the same time the relatively high activity in brown fat was decreased by about 50%. T_3 levels in the fetuses of injected mothers were 42.75 ± 2.25 ng/ml, compared to 27.3 ± 1.8 in the control fetuses. In suckling rats 24 hours after a single injection of 50µg/100 g body weight essentially the same effects in both tissues were observed. At that time blood levels of insulin and glucagon were found to be elevated. These results are very similar to those described previously for corticosteroids (Endocrinol. 103: 1417-1424, 1978). However, T_3 does not lead to a rise in fatty acid synthetase activity in brown fat, while prednisolone does. Thus the mechanisms of action of the two hormones are probably not the same. Our data indicate that T_3 may be involved in the neonatal rise in hepatic PEPcK activity.

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