mal in size and appearance. Subsequent histo-cytologic studies showed no anatomic abnormalities. Usual doses of endocrine replacement medications were sufficient.

Post-hypophysectomy, the patient rapidly improved. At three months, the following changes have occurred: (CLINICAL) 1) skin less pigmented, 2) acanthosis nigricans much improved, 3) liver about half former size, 4) beginning subcutaneous fat deposition. (LABORATORY) 1) serum no longer lipemic, with neutral fat levels returned to normal, 2) liver function tests returned to normal, 3) hyperinsulinism and insulin resistance less severe.

Our pre-hypophysectomy studies showed immunoreactive growth hormone levels to be low normal with no significant increase following intravenous insulin or arginine. These pre- and post-hypophysectomy findings suggest that the central problem involves the pituitary's secretion of an abnormal hormone with melanotrophic and growth hormone properties.

Regulation of growth and plasma growth hormone in a Laron's dwarf. M. JOYCELYN ELDERS, JOHN T. GARLAND, WILLIAM H. DAUGHADAY, DELBERT A. FISHER, and EDWIN R. HUGHES. *Univ. Ark. Med. Ctr., Little Rock, Ark., Washington Univ., St. Louis, Mo., and UCLA, Torrance, Calif.*

Laron identified a group of children with severe growth failure and high levels of immunoreactive human growth hormone (IR-HGH). To investigate why these patients often have elevated HGH, we studied a 7½ year old Saudia Arabian boy with a height of 85 cm (HA 2 yrs) and basal IR-HGH levels of 32 to 84 ng/ml (normal—less than 5 nanagrams per ml). Fasting blood sugars were often in the hypoglycemic range, and hyperglycemia induced by glucose infusion did not suppress his high IR-HGH. The serum IR-HGH was increased markedly by arginine infusion. High dose HGH treatment (7.5 mg q 12 hrs × 9 doses) did not modify his IR-HGH response 1 hour after arginine (increment over control was 111 and 121 ng/ml before and after treatment). Plasma sulfation factor (SF) was low and did not rise with treatment, as it does in the usual HGH deficient patient. Chronic administration of HGH (2.5 mg 3 × per week) produced a modest growth acceleration of 2.6 cm over the 5 months period compared to an expected response of 6.5 to 12 cm per year, in patients lacking HGH.

These studies suggest that the persistently elevated IR-HGH is due to either a lack of SF to suppress the hypothalamic growth hormone releasing factor or that the hypothalamic HGH receptors share the same defects as those receptors responsible for the initiation of SF synthesis. Regardless of the interpretation, the IR-HGH in these patients does not appear to be under the hypothalamic control system demonstrable in normal individuals.

Glucagon stimulation test (GST): Its effect on glucose homeostasis and growth hormone release in the normal and hypopituitary patient. H. LAWRENCE VALLET, CARLOS CINTRON, THOMAS MOSHANG, JR., and ALFRED M. BONGIOVANNI. *Univ. of Pennsylvania Sch. of Med., The Children's Hosp., Philadelphia, Pa.*

Glucagon causes pituitary polypeptide hormone release in patients with normal pituitary function. We have assessed the effect of a standard dose of glucagon, 0.5 mg. I.M., in 17 patients ages 9 mos. to 14 years who presented with short stature of various etiologies. Results reveal that glucagon induces growth hormone (GH) levels equal to or greater than those achieved by either an Insulin Tolerance Test (I.T.T.) or Arginine Tolerance Test (A.T.T.). A 17 mμg/ml difference in GH levels was noted at 90 to 120 mins. after the glucagon injection. Among the normal respondents (≥5.0 mμg/ml rise), there were neither false negative nor false positive tests when compared to a matched I.T.T. or A.T.T. One glucagon non-respondent (≤1.0 mμg/ml) also had a negative exercise tolerance test yet had a blunted A.T.T. One patient with a blunted G.S.T. had a normal I.T.T.

After glucagon, the mean glucose levels of the growth hormone deficient patients were 20 mg% higher than in the normal patients. Their lowest blood sugar occurred later in the test than in the normal and subnormal respondents. A "back-to-back" A.T.T.-G.S.T. done the same day induces two peaks of growth hormone without risk of hypoglycemia, and may be the most reasonable screen for this type of patient. Glucagon may be used to further our understanding of the abnormalities of glucose homeostasis in growth hormone deficient patients.

Growth hormone (GH) as a therapeutic agent in patients with intrauterine growth retardation (IGR). THOMAS P. FOLEY, JR., MAURICE SHAW, ALICE BAGHDASSARIAN, PETER NISSLEY, ROBERT G. THOMPSON, and ROBERT M. BLIZZARD. *Johns Hopkins Univ. Sch. of Med., Baltimore, Md.*

Eleven patients with IGR of unknown cause were studied; 4 of 5 followed for 12–19 months on GH grew significantly. In 9 of 11 the bone age (BA) was significantly retarded. Pretreatment growth rates (GR) were less than expected for chronological age (CA). All secreted normal amounts of GH with arginine infusion and insulin hypoglycemia before and after therapy.

The data is summarized below in 5 patients:

Patient	Birth Wt	Birth Lt	Gestation	Onset of therapy			Growth rate (cm/year)				
							Pre-Rx	on HGH: dose mg/day			
	Gm	Cm	weeks	CA	HA	BA		5mg	2.5mg	2.0mg	1mg
A.W.	1650	48.5	39	9 11/12	6 8/12	6 3/12	4.6	10.2	—	—	7.2
C.V.	1920	43.4	39	8 8/12	3 9/12	6 0/12	5.3	—	—	—	8.0
M.S.	2180	48.5	39	6 6/12	2 10/12	4 6/12	4.2	11.4	—	5.2	5.5
J.S.	1760	42.0	39	4 4/12	1 9/12	2 8/12	5.5	13.4	—	8.9	7.6
G.R.	3104	43.2	39	12 11/12	7 2/12	11 0/12	4.3	—	6.8	—	4.4

Conclusions: (1) Exogenous GH accelerates growth rates in some patients with IGR; (2) Higher doses are required to accelerate growth to the GR attained in patients with GH deficiency; (3) Some patients with IGR with skeletal retardation may be candidates for exogenous GH therapy when available in abundant supply.

Newborn urinary cyclic AMP and developmental renal responsiveness to parathyroid hormone. LOUIE G. LINARELLI. *Mercy Hospital and Children's Hospital of Pittsburgh, Pittsburgh, Pa.* (Intr. by Thomas Oliver).

Since the renal action of parathyroid hormone (PTH) is known to be mediated via 3′,5′-adenosine monophosphate (cyclic AMP), urinary cyclic AMP studies were used to determine proximal tubular maturation. Ten formula fed full-term male infants showed a 30 to 60 fold increase in phosphate clearance and excretion with a 3–4 fold increase in urinary cyclic AMP comparing their first and third day 24-hour urines.

	Phos. Excretion mg/24 hr/1.73 M^2	Phos. Clearance ml/min/1.73 M^2	Urinary CAMP 24 hr nanomoles	Urinary CAMP 24 hr μmoles per gm creat
Mean ± S.E.M.				
Day 1	7.86 ± 2.56	0.09 ± 0.03	53.2 ± 10.89	2.37 ± 0.41
Day 2	443.50 ± 77.12	3.49 ± 0.62	208.6 ± 37.00	6.93 ± 0.96

This 3–4 fold increase in cyclic AMP could reflect increasing PTH renal responsiveness and/or increasing secretion of PTH. One and 3 day old infants and adults were given a one hour PTH infusion (5 μ/Kg/hr) measuring urinary cyclic AMP in time periods before and after the infusions. Peak increases in responses from baseline of cyclic AMP were 1.64 ± 0.34, 7.15 ± 1.15 and 36.30 ± 0.73 μmoles/gm creatinine mean ± range on first day, third day and adults respectively with similar relationships of increasing phosphate excretion and decreasing % TRP. Thus, the development of newborn renal responsiveness to parathyroid hormone is on the cellular cyclic AMP level suggesting increasing maturation of the enzyme adenyl cyclase which forms cyclic AMP from ATP.

Pseudohypoparathyroidism without clinical stigmata. ROBERT M. CORWIN, GAETANO VISCO, and WILLIAM H. BERGSTROM. *State Univ. of New York Upstate Med. Ctr., Syracuse, N. Y.*

Five cases of pseudohypoparathyroidism without the usually associated clinical stigmata of short stature, mental retardation, brachydactylia and moon facies have recently been identified in Syracuse. Four of the cases are in the same family. The familial proband was a 12 year old, previously asymptomatic girl who, following a grand mal seizure, was found to have hypocalcemia, hyperphosphatemia, an elevated alkaline phosphatase and radiologic hyperparathyroidism. She was refractory to parathyroid extract but did respond to large doses of calciferol. Her father, brother, and two of her three sisters were clinically and biochemically normal. However, her 46 year old mother and 20 year old sister had biochemical pseudohypoparathyroidism. Investigation of this family has also revealed a maternal uncle with pseudohypoparathyroidism and a 79 year old healthy maternal grandfather with biochemical evidence of hyperparathyroidism. The fifth case is that of a tall, thin, highly intelligent black male who has been followed for 12 years with a history of grand mal seizures controlled with anticonvulsant medications (Dilantin, Phenobarbital and Mysoline). After a wrist injury, x-rays revealed unsuspected bone resorption. Subsequent studies disclosed hypocalcemia, hyperphosphatemia, elevated alkaline phosphatase, and generalized osteitis fibrosa cystica. He was refractory to parathyroid extract but did respond to large doses of calciferol with complete healing of the bone lesions. These five cases are presented to re-emphasize the fact that pseudohypoparathyroidism need not be associated with clinical stigmata.

Improved prognosis in congenital hypothyroidism treated before three months. Behavior concerns of parents of treated cretins. ALAN KLEIN, STEPHANIE MELTZER, and FREDERIC M. KENNY (Intr. by T. K. Oliver). *Univ. of Pittsburgh Med. Sch., Pittsburgh, Pa.*

We explored the possibility that a critical period exists during the first few months of life, when treatment should be started in order to obtain a normal IQ. Previous publications have not fractionated the first 6 months of therapy for comparison of IQ results by a single test procedure. Thirty-one cretins were tested by Stanford Binet after age 3 years. A significantly higher percentage had IQ > 85 when treated before 3 months (Chi-Square $p < 0.02$) indicating that thyroprevia is most harmful during the period that CNS neuronal number is increasing.

Age in Months When Treated	<3	3-4	5-6	>7
Number of patients with IQ > 85	7	1	2	0
Number of patients with IQ < 85	2	7	6	6

Questionnaires disclosed twice as many behavior concerns in parents of cretins with IQ < 85 than in those with IQ > 85 whose parents had no more worries than those of age matched normals. Parents had anxiety about punishment of these children who were characterized as "high strung, stubborn, contrary" and whose "feelings were easily hurt." Concern was high regarding future education and jobs.

Since clinical diagnosis of cretinism is difficult during the first 2 months of life, and since it is as common (1:8,000 live births) as phenylketonuria (1:10,000), a routine screening procedure is warranted. Systematic psychological counseling should be an integral part of therapy.

Placental transfer of thyronines and thyrotropin in sheep. JEAN H. DUSSAULT, JOSEPH J. DISTEFANO, and DELBERT A. FISHER. *UCLA Sch. of Med., Harbor General Hosp., Torrance, Calif.*

Data in a number of species suggest that placental transport of thyronine is limited in extent. Data regarding placental passage of TSH is indirect but suggests little or no transfer. The present studies were conducted to quantify T4, T3 and TSH transfer directly in both the maternal-fetal and fetal-maternal directions. Indwelling exteriorized fetal catheters and maternal jugular vein catheters were placed in pregnant sheep. Simultaneous tracer doses of 131-I-T4 and 125-I-T4 were injected into the fetus and mother, respectively, in one study (6 animals); 131-I-T3 and 125-I-T3 in another (6 animals); and 131-I-BTSH and 125-I-BTSH in a third (5 animals). Serial blood samples were collected for periods up to 96 hours. These were extracted with butanol (for T3 and T4) or ppt with specific BTSH antibody (for TSH), and counted in a double isotope counting system to assess placental transfer of labeled hormones. There was no significant transfer of labeled T4 or TSH. However significant transfer of labeled T3 occurred in both the fetal-maternal and maternal-fetal directions. By assessing maternal and fetal T3 kinetic data and assuming exchange between two compartments it was possible to quantify this transfer. Fractional transfer rates were 0.045 and 0.0023 hr.-1 in the fetal-maternal and maternal-fetal directions respectively. Since hormone pools and turnovers were measured it could be estimated that about 2 μg T3 were transferred daily in both directions. This approximated 0.5% and 2.0%, respectively, of total daily maternal and fetal thyronine turnover. These data further support the view that the fetal pituitary-thyroid axis functions autonomously of the maternal system.

Neonatal and early childhood hyperthyroidism: An expression of hereditary Graves disease. DOROTHY R. HOLLINGSWORTH, C. CHARLTON MABRY, and JOHN M. ECKERD. *Univ. of Kentucky, Lexington, Ky.*