(HGH). L. BAKER, A. I. WINEGRAD, H. L. VALLET, R. S. CLEMENTS, G. MORROW and A. M. BONGIOVANNI. *Univ. of Pennsylvania Sch. of Med., Philadelphia, Pa.*

A 9½ year old girl has had severe reactive hypoglycemia since age 11 months. No evidence of a pancreatic adenoma was found on laparotomy. On recent re-evaluation, abnormalities of CHO metabolism were documented in both the fed and fasting states. Oral GTT consistently demonstrates a slightly elevated fasting level, a 2 hour value in excess of 140 mg.%, and a 5 hour value less than 40 mg.%. Plasma insulin concentration peaked at 1½ to 3 hours (50–80 μU/ml) but are still elevated at the 5th hour. This pattern was unaltered by therapy with Diazoxide or Tolbutamide. Symptomatic hypoglycemia consistently develops on prolonged fasting (20–24 hours). The plasma FFA, ketone and amino acids fail to show an appropriate response to fasting. Fasting hypoglycemia is rapidly corrected by the administration of glycerol, a substrate for gluconeogenesis. Despite normal growth, plasma HGH was undetectable following spontaneous hypoglycemia or exercise, or during sleep. Maximal stimulation with sequential insulin-arginine tolerance tests gave a subnormal response (5 mμg/ml). Acute HGH therapy prevented fasting hypoglycemia, and plasma FFA and ketones rose appropriately. Reactive hypoglycemia was also corrected. This appears to be a new hypoglycemic syndrome.

Direct "adrenergic" activity of diazoxide on insulin release. IAN M. BURR, ERROL B. MARLISS, and ALBERT E. RENOLD (Intr. by David Karzon). *Vanderbilt Univ. Med. Sch., Nashville, Tenn., and Inst. de Biochim. Clin., Geneva, Switzerland.*

The direct effects of the hyperglycemic agent diazoxide (D), on dynamic insulin (IRI) release from rat pancreas in vitro have been compared with those of epinephrine (E). Like E, D produces dose dependent suppression of the primary (I) and secondary (II) phases of glucose (G) induced IRI release, an effect partly reversed by α adrenergic blockade. Conversely, continuous stimulation with 10 μg/ml + 20 μg/ml phentolamine produces a biphasic pattern of IRI release similar to that observed with β adrenergic stimulation with l-isopropylnorepinephrine, either agent alone being ineffective. As for E, prestimulation with low doses of D selectively enhances subsequent G induced I, an effect abolished by β adrenergic blockade during prestim. In contrast to E, prestim. with higher concentrations of D enhances both phases of G induced IRI release, an effect which is not abolished by α adren. blockade during prestim. Conclusions: (a) D can stimulate both α and β adrenergic receptor activity in B cells which may explain both the direct inhibition of IRI release by D and the apparently paradoxical enhancement of IRI release on cessation of D therapy. (b) Some effects of D are not realized through direct effects on adrenergic receptors.

Immunoassay of glucagon-like activity in infants and children. D. Y. MURTHY and ELEANOR COLLE. *Montreal Children's Hosp.-McGill Univ. Research Inst., Montreal, Que., Can.*

Glucagon levels were assayed with a guinea pig antisera which cross reacts minimally with an extract of dog gut. Column chromatography of pools of plasma revealed three peaks. Peak I, which behaved like gut reacting glucagon-like activity accounted for less than 20% of glucagon-like activity in the fasting and post-arginine infusion pools. Peak II is the major peak and behaves like pancreatic glucagon on dilution. Peak III reveals minor differences on dilutional studies. With this antisera, the mean level in normal fasting prepubertal children was 669 ± 62 pg/ml and in fasting adolescent diabetic children in good control 333 ± 46 pg/ml. Following intravenous arginine infusion a 2 fold or greater rise was seen in glucagon-like activity in 5 children without abnormalities in carbohydrate tolerance, in 5 newly diagnosed diabetics, in 5 children with asymptomatic hyperglycemia, in 5 children with small stature secondary to intrauterine growth retardation, and in 1 child with growth hormone deficiency. Two children treated with chlorpropamide for 1 year for diabetes insipidus also had normal rises despite impaired insulin release. Values for glucagon-like activity were elevated in cord blood (mean 1288 ± 146 pg/ml) and in plasma from normal newborn infants before feeding (mean 1412 ± 55 pg/ml). Three of five infants of diabetic mothers and three of six infants with blood group incompatibility had levels greater than 2000 pg/ml.

Hormonal aspects of post-hypoglycemic hyperglycemia (Somogyi effect) in diabetic children. ERIKA BRUCK and MARGARET MACGILLIVRAY. *State Univ. of N. Y. at Buffalo, Sch. of Med., Children's Hosp. of Buffalo, Buffalo, N. Y.*

The causes of hyperglycemia and acetonuria which may alternate with hypoglycemia in diabetic children are poorly understood. To evaluate the hormonal basis of the "Somogyi effect" in 3 "brittle" diabetic children, glucose, growth hormone (HGH) and cortisol levels in blood were measured hourly or half-hourly, and urinary catecholamine excretion in 2-hourly collections, for several 24–48 hour periods. Profound hypoglycemia (7–40 mg%) alternating with prolonged hyperglycemia was demonstrated at unpredictable times, even though fasting glucose was normal or elevated. HGH levels increased sharply, sometimes to as much as 30–75 mμg/ml, with hypoglycemia or following every sharp fall in glucose, even when the latter remained in the hyperglycemic range. These peaks of HGH were usually followed by marked hyperglycemia. Plasma cortisol levels varied erratically without consistent relationship to glucose levels. Rises in catecholamine excretion (to 4–12 μg/hr) occurred following hypoglycemia and also independently of it, but did not always cause elevation of glucose. With gradual reduction of insulin dosage, the control of the diabetes improved, and in one patient who was profoundly stuporous, the mental state improved dramatically. These studies emphasize the importance of determining blood sugar concentration at frequent intervals since hypoglycemia may go unrecognized for years if the standard sampling times are adhered to. The hormonal data support the concept that growth hormone release in response to hypoglycemia in the diabetic is an important factor in producing hyperglycemia and insulin resistance.

Generalized lipodystrophy (lipoatrophic diabetes): Evidence for abnormal pituitary function. C. CHARLTON MABRY and DOROTHY R. HOLLINGSWORTH. *Univ. of Kentucky, Lexington, Ky.*

Long term observations and studies on two unrelated children with generalized lipodystrophy suggest a pituitary-endrocrine disorder with abnormal melanotropic growth-hormone-like secretion as the probable cause. Our patients have the advanced characteristics of generalized lipodystrophy which include loss of all body fat, skeletal and muscle overgrowth, hepatomegaly due to neutral fat infiltration, insulin resistant hyperglycemia, hyperlipemia, hyperpigmentation and greatly elevated levels of immunoreactive insulin.

We subjected a 13-year-old girl with generalized lipodystrophy to total surgical hypophysectomy. The pituitary gland was nor-

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.