

Effects of glutamine deficiency on purine metabolism in the Lesch-Nyhan syndrome. KARI O. RAIVIO and J. EDWIN SEEG-MILLER. *Univ. of Calif., San Diego, Calif.*

Glutamine (GLN) is the amino donor in two reactions of *de novo* purine synthesis and in the formation of guanylic from xanthylic acid (XMP). When confluent cultures of fibroblasts from normal individuals or from patients with the Lesch-Nyhan syndrome (LN) are maintained in GLN-free medium for 24 hours, their rate of *de novo* synthesis decreases to one-tenth of control cultures. Addition of GLN causes a 5–15-fold stimulation in both types of cells, but at comparable levels of GLN the rate in LN fibroblasts remains 2–5 times higher than normal. In GLN-free medium, LN cells convert 50% more adenine-<sup>14</sup>C to nucleotides than do normal cells. Of the radioactivity taken up, 1.1% is diverted to guanine nucleotide synthesis in the normals, and 2.8% in LN fibroblasts (sum of radioactivity in guanine nucleotides, XMP, the corresponding nucleosides and bases). In GLN-free medium, XMP, xanthosine, and xanthine contain 67% of this total in the mutants and 43% in the normals. Addition of GLN brings about a decrease in the total incorporation into the components of the pathway, but a net increase in guanine nucleotide synthesis, as only 4% of the radioactivity is now found in the xanthine compounds in the mutants and 8.8% in the normals. The results show that the availability of GLN can be rate-limiting not only to *de novo* purine synthesis, but also to guanine nucleotide formation at the XMP aminase reaction. LN cells appear to be more sensitive to GLN deprivation in this reaction, and yet are solely dependent on it for guanine nucleotide synthesis, as they are grossly deficient in hypoxanthine guanine phosphoribosyltransferase activity.

Pyruvic decarboxylase inhibition in ketoaciduria. DERRICK LONSDALE, J. WAIDE PRICE, and RAYMOND J. SHAMBERGER (Intr. by Robert Schwartz). *Cleveland Clinic, Cleveland, Ohio.*

A patient with intermittent episodes of cerebellar ataxia has been described (*Pediat.* 43:1025, 1969). The child excreted large amounts of urinary pyruvic acid during an episode which was studied in detail. Fibroblast tissue culture cells were assayed for pyruvic decarboxylase and found to contain a low concentration of this enzyme. Further examination of urine collected during the ataxic episode revealed that alanine was excreted in amounts proportional to that of pyruvic acid and that both metabolites were in concentrations inversely proportional to those of glutamic acid and aspartic acid. A child with late diagnosed, and hitherto untreated, phenylketonuria (PKU) was examined and found to have a high serum phenylalanine concentration and ketoaciduria. She was treated with a phenylalanine deprivation diet and urines collected in day and night 12-hour contiguous sequence. As the serum phenylalanine concentration fell there was a concomitant decrease in greatly elevated concentrations of urinary pyruvic acid into the normal range together with a steady increase in concentrations of urinary glutamic acid. These observations suggested that inhibition of pyruvic decarboxylase could be an important mechanism in PKU as well as other ketoacidurias and that such a mechanism might involve the metabolism of glutamic acid. Experiments were carried out and showed that authentic  $\alpha$  iso caproic acid and phenylpyruvic acid produce a marked decrease in the activity of pyruvic decarboxylase *in vitro*.

Preferential hepatic galactose uptake in the newborn. LAWRENCE F. X. KELLY, RICHARD TRABERT, DAVID ABRAMSON, N. VILDAN

ERKAN, ARLINE MARTIN and MALCOLM M. MARTIN. *Georgetown Univ. Sch. of Med., Washington, D. C.* (Intr. by Philip L. Calcagno).

Previous studies demonstrated impaired carbohydrate tolerance with a delayed and excessive rise in plasma glucose and insulin following oral glucose in healthy full term newborns less than 24 hours of age. To evaluate the role of the liver in determining carbohydrate tolerance, galactose tolerance tests were carried out in 6 full term infants of comparable age. Following a 3 hour fast, galactose (2 gr/Kg) was given by gavage. Blood samples were obtained from umbilical vein and from heel sites before and half-hourly to 3 hours following galactose feeding. Results indicate a rapid rise in total sugar and glucose with an early peak following the galactose feeding with little change in insulin concentration in either umbilical or capillary blood. Paired data analysis revealed a significant difference between total sugar and glucose in umbilical venous blood which was absent in capillary blood. Similarly there was a significant difference between umbilical venous and capillary blood total sugar but no difference in glucose. The data indicate rapid hepatic uptake of galactose as opposed to glucose without change in circulating insulin. The concomitant rise in glucose suggests almost immediate conversion of galactose to glucose in the newborn, which is not seen in older children.

#### ENDOCRINOLOGY

Idiopathic hypoglycemia—a defect in hypothalamic ACTH-releasing factor secretion. MALCOLM M. MARTIN and ARLINE L. A. MARTIN. *Georgetown Univ. Sch. of Med., Washington, D. C.* (Intr. by Philip L. Calcagno).

Corticotropin releasing factor (CRF) deficiency has not previously been demonstrated as a cause of hypoglycemic convulsions. We have recently studied 3 children who justify such a diagnosis. One child moreover has an identical twin who provided the ideal control in the various test situations. The presence of a disorder in ACTH release was suggested by the absence of a response in plasma cortisol and plasma ACTH to insulin induced hypoglycemia as measured by radioimmunoassay, impaired prompt water diuresis, lack of elevation in urinary 17-OHCS following metyrapone administration despite adequate 11-B-hydroxylase inhibition and normal adrenocortical activation by exogenous ACTH. Normal insulin and growth hormone responses to glucose, arginine, tolbutamide and glucagon administration as well as catecholamine release by insulin induced hypoglycemia confirmed the isolated nature of the defect in keeping with the presence of a normal growth pattern and normal thyroid indices. That the defect is one of hypothalamic activation of ACTH release rather than isolated ACTH deficiency was confirmed by the release of ACTH and rise in plasma cortisol following vasopressin administration. Two children had a history of low birth weight for gestation age. The third infant was born postmature with respiratory distress. The available evidence suggests that this is an acquired defect rather than a genetically determined abnormality. Hypoglycemia due to a defect in hypothalamic activation of ACTH release may provide the explanation for fasting hypoglycemia and convulsions in children otherwise unexplained or masquerading as ketotic hypoglycemia.

A new hypoglycemic syndrome: Fasting and reactive hypoglycemia, normal growth and deficient plasma growth hormone

(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  $\mu$ U/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  $\mu$ g/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  $\alpha$  adrenergic blockade. Conversely, continuous stimulation with 10  $\mu$ g/ml + 20  $\mu$ g/ml phentolamine produces a biphasic pattern of IRI release similar to that observed with  $\beta$  adrenergic stimulation with 1-isopropyl-norepinephrine, either agent alone being ineffective. As for E, prestimulation with low doses of D selectively enhances subsequent G induced I, an effect abolished by  $\beta$  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  $\alpha$  adren. blockade during prestim. Conclusions: (a) D can stimulate both  $\alpha$  and  $\beta$  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  $669 \pm 62$  pg/ml and in fasting adolescent diabetic children in good control  $333 \pm 46$  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  $1288 \pm 146$  pg/ml) and in plasma from normal newborn infants before feeding (mean  $1412 \pm 55$  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  $m\mu$ g/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  $\mu$ g/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-endocrine 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-