METABOLIC RESPONSE TO I.V. GLUCAGON IN CHILDREN WITH CHRONIC LIVER DISEASE L. Linarelli, H. Rubin, K.G. Pai, J. Bobik, C. Bobik and A. Drash, Univ. of Pittsburgh Sch. of Med., Mercy Hosp., Children's Hosp., Dept. of Ped.

Studies were performed to evaluate glucose homeostasis in children with intrahepatic biliary hypoplasia (IBH) with chronic cholestatic syndrome and growth retardation. Eight I.V. glucagon tolerance tests (30 μg/kg) on five IBH patients (4-12 yrs of age) were compared to 8 controls. Fasting (14-16 hr) glucose was lower in IBH (67 ± 4 mg% vs 80.8 ± 3.67; $p < 0.025$), and peak rise was significantly less (107 ± 10.6 vs 147 ± 7.9; $p < 0.01$). Baseline urinary cyclic AMP levels in IBH vs controls (5.8 ± 2 M ± S.E.M. nmoles/mg creatinine vs 4.5 ± 0.4) and 2 hour excretion response to glucagon (31.1 ± 3 vs 28.6 ± 5.2) were not significantly different. Insulin response to glucagon were similar in IBH vs control. Glucagon has previously been shown to lower plasma gluconeogenic amino acids as a indication of hepatic uptake and gluconeogenesis. Fasting plasma alanine was not significantly different in IBH vs control (210 ± 38 umoles/L vs 245 ± 40). Controls had a significant delta decline at 30 minutes post-glucagon of 100 umoles/L for alanine, 66 for glycine and 39 for glutamine plus asparagine. IBH patients failed to elicit a consistent reduction in gluconeogenic amino acids. These studies suggest that hepatic gluconeogenesis and glycogen storage are impaired in chronic liver disease. The noted cyclic AMP response may reflect adequate adenyl cyclase activity in spite of hepatocellular damage.

BENEFIT OF VIGOROUS ANTICEREBRAL EDEMA THERAPY IN REYES SYNDROME - PROSPECTIVE STUDY. F. H. Lovejoy, A. L. Smith, M. Bresnan and C. Lombroso (Intr. by David H. Smith) Children's Hospital Medical Center, Dept. of Med., Boston, Mass.

Our previous studies (1968-1971) have allowed identification of five clinical stages in patients with Reyes Syndrome based on the degree of central nervous system involvement. All patients with an illness limited to stages I to III lived; while those with disease progressing to stage IV had been associated with a poor outcome (two of 19 lived, both severely impaired neurologically). Stage IV disease, occurred in 10 of 15 patients followed prospectively (1971-1973). Intensive therapy to combat cerebral edema (mannitol in doses up to 6g/kg/day, glycerol 6g/kg/day, dexamethazone at 0.5mg/kg/day and fluid restriction to 40ml/kg/day) permitted survival in four of six stage IV patients. This is in contrast to death occurring in three of four stage IV patients treated with conventional anticerebral edema therapy. Clinical symptomology (usually a reversal to an improved stage) and EEG status improved within hours of vigorous therapy. In these five survivors of stage IV disease; three are normal 2 to 22 months following onset of illness; one has mild hemiparesis and memory deficit, and one with severe neurologic impairment (hemiballisimus and hemiparesis) is gradually improving. Intensive therapy directed towards decreasing intracranial pressure has allowed survival of children with stage IV Reyes Syndrome.

PANCREATIC ALPHA AND BETA CELL FUNCTION IN CHILDREN WITH CYSTIC FIBROSIS (CF). Barbara Lippe, Mark Sperling and Richard Dooley. (Intr. by Solomon A. Kaplan). UCLA Sch. of Med., Dept. of Ped., Los Angeles.

Inappropriate plasma glucagon responses to oral glucose have been reported in diabetes (DM), and it has been suggested that alpha cell dysfunction is a characteristic of genetic DM. To further evaluate this hypothesis, plasma glucagon and insulin were measured in children with CF following standard oral glucose (GTT) or intravenous arginine (ATT) tolerance tests. CF patients were classified as being normal (Group A) or variably abnormal (Group B) on the basis of the glucose responses to the GTT. During the GTT plasma glucagon declined by a mean of 64 ± 22 pg/ml in A ($p < 0.05$) and by 34 ± 7 pg/ml in B ($p < 0.01$), (A vs. B ns.) while plasma insulins peaked at a mean of 28 ± 5 μU/ml in A and 48 ± 15 μU/ml in B. The ATT resulted in a significantly greater glucagon response at 30 min. in A than B, 622 ± 39 pg/ml vs. 238 ± 74 pg/ml ($p < 0.005$); while the peak insulin responses were low in both groups, 13 ± 2.6 vs. 21 ± 2.2 μU/ml. These data suggest (1) suppressibility of glucagon to glucose persists despite carbohydrate intolerance in CF patients in contrast to reported non-suppressibility in genetic DM. (2) Insulin responsiveness is obtunded in CF patients in both groups. (3) CF affects pancreatic alpha and beta cell function as well as exocrine function.

GENERALIZED LIPODYSTROPHY:EFFECT OF CEREBRAL DOPAMINERGIC BLOCKING AGENT (PIMOZIDE). C.C. Mabry, G.V. Upton, A. Corbin, D.R. Hollingsworth, Univ. Kentucky Col. Med., Lexington, Yale Univ. Sch. Med., New Haven, and Wyeth Lab., Philadelphia.

Generalized lipodystrophy (GLD), characterized by loss of subcutaneous and other fat, skeletal/muscle overgrowth, neutral fat hepatomegaly, genital enlargement, gonadal failure, hyperpigmentation, acanthosis nigricans, hyperlipidemia, hyperglycemia, and hyperinsulinism, is associated with detectable hypothalamic regulatory hormones in plasma (J Pediat 82:625, 1973).

Reasoning that GLD is a disorder of hypothalamic dysfunction dependent on catecholaminergic mechanisms, and using our earlier experience with chlorpromazine, we administered Pimozide to a 7-year-old girl with GLD (8 mg/day for 16 mo). Pimozide (a diphenylbutylpiperidine used as a neuroleptic) is a selective inhibitor of cerebral dopaminergic receptors.

Effects over 16-months were: a) immediate and sustained diminution of luteinizing releasing hormone and corticotropin releasing hormone to zero or trace plasma levels, b) return of normal response to intravenous ACTH (Acta Endocr 73:437, 1973), c) return of liver function and size to normal or near normal with abatement of abdominal pain, d) reversal of skin and hair changes, e) return of subcutaneous fat to face and back as shown by appearance and biopsy (0.5 cm thick).

These results 1) support the concept of diencephalic involvement in GLD, 2) indicate that Pimozide impairs the synthesis/release of hypothalamic regulatory hormones, and 3) suggest that GLD is amenable to meaningful treatment.

AMINOACIDURIA AS AN INDICATOR OF PHENYLALANINE AND/OR CALORIC DEFICIENCY IN TREATED PKU PATIENTS, Derrick Lonsdale, (Intr. by Robert Schwartz) Cleveland Clinic, Dept. of Ped., Cleveland, Ohio.

Successful treatment of phenylketonuria (PKU) depends upon neonatal diagnosis and optimum combination of dietary phenylalanine and calories, especially in the first 3 months. Head circumference increases and "catch up" growth occurs with such dietary optimum. This acceleration requires appropriate changes in dietary phenylalanine and calories. Low serum phenylalanine concentrations (< 2 mg/100 ml) indicate increased phenylalanine requirement but increased caloric needs are harder to determine. Of 19 infants with PKU, identified by neonatal screening and treated by phenylalanine restriction since January 1967, 15 excreted increased amounts of urinary amino acids, usually glycine, alanine, methionine and phenylalanine, but occasionally others as well. Unappeased appetite, deceleration in head circumference change, and aminoaciduria were usually corrected by increasing dietary phenylalanine. In some cases, when the serum phenylalanine was high, improvement in these criteria was accomplished by increasing dietary calories without increasing phenylalanine intake. Diet prescriptions during the first 3 months required phenylalanine increases to as high as 125 mg/kg body wt. and calories to as high as 185/kg. Appropriate decreases were possible after 4 to 6 months and allowances per unit body wt. were usually stable after 1 year. Aminoaciduria appeared to reflect an improper dietary balance.

GLYCEROL INTOLERANCE: A NEW SYNDROME. Noel K. Maclaren, Carolyn Cowles, Pinar Ozand and Marvin Cornblath, Univ. of Maryland Sch. of Med., Dept. Ped., Baltimore.

A 3 yr old boy had numerous episodes of fatigue, irritability, pallor and sweating dating from 11 mo. of age when he had an episode of symptomatic hypoglycemia with ketonuria. His height and weight were below the 3rd percentile. No hepatomegaly or cataracts were found. Intellectual development, liver and renal functions, electrolytes, T_4, hGH and cortisol values were normal. He manifested euphoria, mental confusion, drowsiness, nausea and vomiting 1-5 hrs after oral glycerol in doses of 0.5-1 gm/kg. Oral medium chain triglycerides (1 gm/kg) had similar effects. Once, oral glycerol (1 gm/kg) also provoked hypoglycemia with a decline in blood lactate. A 16 1/2 hr fast also induced hypoglycemia, unresponsive to glucagon. IV glycerol (0.09 gm/kg) induced an immediate loss of consciousness with no change in blood glucose. He recovered spontaneously after 30 min. IV fructose (0.25 gm/kg) was tolerated normally. Leukocytes showed normal activity for fructose-1, 6-diphosphatase, glycerol kinase and glycerol phosphate dehydrogenase. However, plasma dopamine β hydroxylase activities were low and fell significantly following IV or oral glycerol. The restriction of dietary fat intake improved his physical and mental activities. These observations suggest a unique, yet undefined metabolic intolerance to glycerol. Supported by grants from the John A. Hartford Foundation and NIH #HD 03959-06 and HD 06291-03.