1206 PYRUVATE DEHYDROGENASE DEFICIENCY WITH LACTIC ACIDOSIS AND HYPERAMMONEMIA: RESPONSES TO DICHLOROACETATE AND BENZOATE. Kenneth McCormick, Rose M. Viscardi, Brian Robinson. (Spon. by Gilbert B. Forbes). U. of Rochester Med. Center, Dept. Pediatrics, Rochester, NY, U. of Toronto, Toronto Childrens' Hospital, Toronto, Canada.

A full term neonate developed hypotonia, profound lactic acidosis (HCO_3^- 3 mM, lactate 10mM) and persistent hyperammonemia (896µg/dl) at age 8 hr. Despite peritoneal dialysis, blood NH_3 remained elevated (>200µg/dl); IV benzoate was helpful, and hippurate could be detected in the peritoneal fluid. Multiple GLC studies of urine revealed only massive quantities of lactate; urinary orotic acid was minimally elevated. Serum alanine was grossly elevated. Skin fibroblast studies: normal carboxylase enzyme levels, pyruvate dehydrogenase (PDH) 52% of control, whole cell $1\text{-}^{14}C$ pyruvate oxidation 42% of control. As in the other case reports, even a partial PDH deficiency typically causes severe clinical and biochemical disturbances. At age 10 mo, 50 mg/kg oral dichloroacetate (DCA), an inhibitor of the protein kinase which curtails PDH activity, reduced serum lactate and pyruvate by 50% within 2 hr; of interest, DCA also enhanced residual fibroblast PDH activity by 10-15%. However, despite biochemical improvement the patient developed refractory ascites, respiratory failure, progressive cerebral atrophy, and died at age 12 mo.

PDH deficiency should be included in the differential diagnosis of neonatal hyperammonemia and this may be ameliorated by benzoate. DCA should be considered in the treatment of congenital lactic acidosis.

1207 BIOCHEMICAL PROFILES FOLLOWING ASPIRIN ADMINISTRATION IN REYE'S SYNDROME PATIENTS AND CONTROLS. Marvin E. Miller, Janice Cosgriff, Margaret Williams, Kenneth McCormick. (Spon. by Gilbert B. Forbes). U. of Rochester Medical Center, Dept. of Pediatrics, Rochester, NY.

Is aspirin an important factor in the pathogenesis of Reye's syndrome (RS)? We have challenged 11 control individuals (C), 5 first degree relatives of RS patients (FR) and two patients who have recovered from RS (RS-1 & RS-2) with standard doses of aspirin for 12 hrs. (600 mg. q 4 hrs.) while fasting. There were no differences in the preaspirin and postaspirin concentrations of ammonia, glucose, AST, or LDH in the RS patients compared to the controls. However, both RS patients showed increased lactate, decreased pyruvate, and decreased β-hydroxybutyrate concentrations following the aspirin challenge while controls showed an opposite trend as illustrated below:

	LACTATE (mg/dl)		PYRUVATE (mg/dl)		β-HYDROXYBUTYRATE (mM)	
TIME (hrs.)	0	12	0	12	0	12
RS-1	6.5	14.2	.067	.060	.50	.24
RS-2	7.1	7.9	.24	.19	.90	.21
FR (mean±1SD)	9.1±5.0	6.0±2.6	.13±.07	.21±.19	.34±.46	.22±.14
C(mean±1SD)	7.9±4.1	5.8±3.6	.16±.08	.18±.16	.14±.21	.43±.33

These biochemical differences in the RS patients compared to controls suggest an altered cytosolic redox state which is also an indirect index of mitochondrial function. One interpretation of these preliminary observations is that individuals who develop RS may be susceptible to mitochondrial injury when exposed to aspirin during fasting.

●1208 INSULIN DOES NOT STIMULATE GLYCOGEN AND LIPID SYNTHESIS IN ISOLATED FETAL RAT HEPATOCYTES. John D. Miller, Mark A. Sperling, Supriya Ganguli. Department of Pediatrics, Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio 45229.

We have previously reported differential maturation of insulin sensitivity for glucose metabolism and amino acid uptake in fetal rat hepatocytes. Compared to the adult, insulin binding to liver plasma membrane is double in the fetus (32 ± 0.3 vs. 18 ± 2.4% per 50 µgm membrane protein, $p < 0.01$) due to a 3 fold increase in receptor number per unit cell surface area. To study further the role of insulin in fetal metabolism, we examined two established insulin-mediated events in freshly isolated rat hepatocytes: glycogen synthase activity and ^{14}C-acetate incorporation into lipid. Viability of both adult (A) and 21 day fetal (F) hepatocytes was documented throughout the experiments. The glucose-6-phosphate dependent form of glycogen synthase (D) was 2.5 fold higher in F ($p < 0.01$), while the independent form (I) was 50% lower in F compared to A when expressed per mg protein ($p< 0.01$). In A, insulin at 10 and 100 ng/ml stimulated both the D and I forms ($p < 0.05$); %I increased with insulin ($p < 0.05$). No such augmentations occured in F. At concentrations varying from 0-30 mM, the incorporation of acetate into lipid was higher in A; at a fixed medium acetate (5mM), insulin at 100 ng/ml stimulated acetate incorporation in A ($p < 0.025$) but not in F. Thus whereas both insulin-mediated events are demonstrable in A they are not present in F despite higher insulin receptor numbers per cell surface area. These results further suggest a dissociation between insulin receptor binding and insulin mediated glucose or lipid metabolism in isolated fetal rat hepatocytes.

●1209 TREATMENT OF HYPERPHENYLALANINEMIA SECONDARY TO A DEFICIENCY OF BIOPTERIN WITH REDUCED PTERINS. Joseph Muenzer, Sheldon Milstein, James Sidbury, Stanley Berlow, and Seymour Kaufman. National Institutes of Health, Bethesda, MD, Univ. of Wisconsin, Madison, WI

A patient (T.D.) with hyperphenylalaninemia caused by a defect in tetrahydrobiopterin synthesis (NEJM 299: 673, 1978) was treated with 6-methyltetrahydrobiopterin ($6MPH_4$) and tetrahydrobiopterin (BH_4) to compare effectiveness. The initial trial of orally administered $6MPH_4$ at 12 mg/kg/d resulted in an excellent clinical response. After 8 mo of treatment $6MPH_4$ was stopped because of elevated liver enzymes (SGOT 324, SGPT 468). The liver function tests returned to normal within 1 mo of stopping $6MPH_4$. Within 3 days of a second trial of $6MPH_4$ at 12 mg/kg the liver enzymes were abnormal (SGOT 119, SGPT 348). $6MPH_4$ was then tappered to 4 mg/kg, but deteriorating clinical function required restarting L-dopa + 5-HT to stabilize the clinical status. Treatment with orally administered BH_4 (11 mg/kg) resulted in dramatic clinical response similar to $6MPH_4$ treatment, but without any evidence of liver toxicity after 1 mo of treatment. BH_4 and $6MPH_4$ (~12mg/kg) caused a lowering of plasma phenylalanine to 1 to 2mg/dl within 1 wk of treatment from pre-treatment levels of 5-10 mg/dl. Measurement of the reduced pterins in plasma by HPLC showed peak levels of $6MPH_4$ about 14-fold higher than BH_4 after oral doses of 4 mg/kg. CSF neurotransmitter metabolites were measured by HPLC on different treatment schedules. The neurotransmitter metabolites levels were not correlated with neurological data.

†1210 L-CARNITINE SUPPLEMENTATION IN SYSTEMIC CARNITINE DEFICIENCY. Michael L. Netzloff, Loran L. Bieber, Michigan State University College of Human Medicine, Departments of Pediatrics/Human Development and Biochemistry, East Lansing, MI.

A 7 3/12 year old white male with systemic carnitine deficiency secondary to renal carnitine loss from Fanconi syndrome was studied on L-carnitine supplementation. A solution of L-carnitine, 10 g. per 100 ml., was supplied by Sigma-Tau, Inc., (723 North Beers Street, Holmdel, N.J. 07733). Following 5 months of supplementation with 250 mg. L-carnitine p.o., q.i.d., the patient had improvement in his muscle strength and ability to ambulate and climb steps. Mental retardation and convulsions, thought to be related to severe hypoglycemia during his initial Reye's syndrome-like presentation with carnitine deficiency, did not improve on carnitine therapy. The renal loss of electrolytes, calcium, phosphate, glucose and amnio acids, and serum electrolytes, calcium, phosphate, bicarbonate and blood PH were unchanged by the treatment with L-carnitine. In addition, scalp hair growth was noted for the first time in his life, and his hearing improved. Serum free carnitine increased from 3.46 to 10.7 µM and total carnitine from 9.58 to 24.7 µM during the extended carnitine supplementation; urine free carnitine loss also increased from 140 to 235 µM, as did total carnitine loss from 237 to 340 µM. Despite increased renal loss of carnitine during oral supplementation, the improved serum carnitine levels and increased muscle strength indicate that sufficient L-carnitine is retained to provide effective oral treatment.

1211 INSULIN INFUSION BY THE ARTIFICIAL ENDOCRINE PANCREAS (AEP). J.F. Nicholson, T. Stoller, Columbia University College of Physicians & Surgeons, Departments of Pediatrics & Pathology, New York City, New York.

AEP control of Type I Diabetes Mellitus (IDDM) generally employs greater amounts of insulin IV than are administered SC. This has been attributed to the use of AEP constants that dictate excessive insulin infusion when blood glucose is rising postprandially, i.e. more than is required for saturation of receptors.

In seven IDDM's, aged 10-21 years, studied because of high SC insulin requirement (1.5 u/kg/d) or glycohemoglobin 16% (normal 5.1-8.5%), or clinical instability, AEP infusion of insulin using high response constants averaged 1.83 u/kg/d (1.33-2.66) without inducing significant hypoglycemia. In one subject undergoing repeat study using high response constants with maximum insulin infusion limited to 0.1 u/kg/hr, postprandial insulin administered was less with similar postprandial blood glucose values, but 24 hour mean blood glucose (MBG) was higher (117 vs. 95) due to increased interprandial blood glucose and insulin/kg/d unchanged (1.35 vs. 1.33). In a second subject studied with maximum insulin infusion at 0.1 u/kg/hr, insulin infused was 1.74 u/kg/d and control of blood glucose was poor (MBG-149), the best period of control being MN-8AM, during which period maximum insulin infusion was given five times without oral intake.

Thus, while high response constants may yield excessive insulin infusion by AEP postprandially, high AEP insulin infusions in our patients are dictated in significant part by insulin requirements not related to meals.