1236 MEDIUM CHAIN ACYL-CoA DEHYDROGENASE (MCD) DEFICIENCY. L. Weber, C. Francomano, S. Brusilow, D. Valle, F. Frerman, and S. Goodman. Johns Hopkins Univ Medical Sch, Dept Pediatrics, Balt; Medical Col Wisc, Dept Microbiology Milwaukee; Univ Colorado Medical Sch, Denver.

We have studied a 6 month old female who had two episodes of lethargy, hepatomegaly, metabolic acidosis, and hypoglycemia without ketosis. She had persistent hypocarnitinemia (avg free 3.6 μ M, ester. 4.7 μ M; nl free 48+8, ester. 6+3). Dicarboxylic aciduria (C6-10) was present during but not between episodes. Extracts of her cultured skin fibroblasts had deficient MCD activity: patient < 0.09 mU/mg; controls (n=9) 1.85-3.66. Activities of palmitoyl-, butyryl- and isovaleryl-CoA dehydrogenases were normal. We compared her response to a 12 hour fast before and after 1 month of therapy with 100mg/kg/d L-carnitine (C).

Fast hours	sympt	gluc	HCO ₃	free C ester.	C 8-OHB	AcAc
pre-C	0	nl	72	16	3.0	3.3
12	coma	40	12	3.8	21.5	305
on -C	0	nl	86	18	50.8	16.8
12	nl	84	20	47.6	35.2	966

Also, pre-C fasting induced marked C6-10 dicarboxylic aciduria accompanied by accumulation of C10-14 fatty acids in plasma. On C, urinary dicarboxylic acids peaked at <20% of pre-C levels with little or no accumulation of C10-14 fatty acids in plasma.

We conclude 1) MCD deficiency is associated with episodic acidosis, dicarboxylic aciduria and C deficiency; 2) administration of C improved tolerance to fasting; 3) care should be taken to distinguish MCD deficiency from other causes of C deficiency.

1237 ALTERATIONS OF GLUCONEOGENESIS IN VIVO BY GLYCEROL-3-PHOSPHATE: EFFECTS OF EARLY MALNUTRITION. Raul A. Wapnir, Lily Stiel and Fima Lifshitz. N. Shore Univ. Hosp., Cornell Univ. Med. Coll., Dept. of Peds., Manhasset, NY.

The in vivo effects of glycerol-3-phosphate (G3P) on gluconeogenesis from alanine (Ala) were investigated in well (C) and malnourished (M) rats. Sixty to 80 g Wistar rats were made M by feeding a 4% protein (Prt), 54% carbohydrate (Cho) diet for 4 weeks. C were fed a diet with 23% Prt and 63% Cho. Both groups received equal amounts of fat, vitamins and minerals. After an overnight fast the rats received a single i.p. dose of Ala (1 g/kg), with or without prior priming with 2 g/kg G3P, 30 min before Ala. Blood glucose (Glc) levels were monitored for 2 hr and noted as changes over baseline. The results indicate: (1) Both groups of rats produced Glc from Ala at the same rate (F=2.89; df=1,60; NS). (2) When G3P was injected before Ala, blood Glc declined in M rats to levels below baseline beginning 60 min after Ala administration (F=69.8; df=1,60; P<0.001, compared to Ala alone). C rats had no inhibition of Glc formation by G3P. Conclusions: in M rats, G3P administration inhibits normal gluconeogenesis from Ala, in contrast to C rats, in which both substrates show no interaction. Therefore, these data support the view that nutritional status may play a role in tolerance to glycerol, the metabolic precursor of G3P, especially early in life.

1238 GLYCOGEN IN FETAL LAMB LIVER IS INCREASED DURING CHRONIC HYPERGLYCEMIA AND HYPERINSULINEMIA. David Warburton. (Spon. by T.G. Keens). Neonatal-Respiratory Disease Division, Childrens Hospital of Los Angeles, Dept. Pediatrics, University of Southern California, Los Angeles.

I studied the developmental profile of glycogen, glycogen synthase and phosphorylase in livers of control fetal lambs at 123, 131, and 142d gestation (term 150d) and in the livers of their twins given intravenous glucose (16±2 mg/kg/min, M±SE) from 112d onwards. Serum glucose (34±2 mg/dl) and insulin (47±11 μ U/ml) in the glucose treated fetuses were higher than serum glucose (19±3 mg/dl, P<0.01) and insulin (14±2 μ U/ml, P<0.01) in the controls.

	123d	131d	142d	
Glycogen content	492	780	1071	Control
μ g/mg wet wt	319	1997	1307	Glucose
Glycogen synthase a	1.6	1.5	1.5	Control
Nmole/min/mg prot	1.2	2.5	1.5	Glucose
Glycogen synthase a+b	17.5	10.9	13.7	Control
Nmole/min/mg prot	12.6	18.4	11.3	Glucose
Phosphorylase a	3.1	3.9	2.1	Control
Nmole/min/mg prot	8.7	5.1	5.4	Glucose
Phosphorylase a+b	6.6	7.3	7.6	Control
Nmole/min/mg prot	11.8	12.9	9.5	Glucose

Fetal liver glycogen is increased during chronic hyperglycemia and hyperinsulinemia. The enzyme activities were also modified by chronic hyperglycemia and hyperinsulinemia.

1239 IMPAIRMENT OF MITOCHONDRIAL OXIDATION BY CHLORAMPHENICOL. John C. Werner, H. Gregg Schuler, Claudia Kasales, Anne Rannels, Victor Whitman, Raymond R. Fripp, Kathryn F. LaNoue. M.S. Hershey Med. Ctr., Pennsylvania State University, Dept. of Pediatrics, Hershey, PA

To investigate the acute effects of CHL on energy metabolism we have studied its effects on oxidative activity in isolated mitochondria from adult rat and newborn pig hearts. We have previously shown acutely reduced myocardial function in newborn pig hearts in the presence of CHL. Respiratory substrates provided were pyruvate (PYR)/malate (MAL) 7.1/4.7mM, glutamate (GLU) 18mM, durohydroquinone (DHQ) 1.62mM, α -ketoglutarate (AKG) 5mM, and succinate (SUC) 10mM. State 3 (ADP-stimulated) oxidation of PYR, MAL, GLU, and DHQ was unaffected or only mildly affected in the presence of CHL concentrations as high as 500 μ g/ml. Oxidation of AKG and SUC was inhibited 39 and 55% respectively in rat and to a similar degree in pig heart by 50 μ g/ml CHL. State 4 oxidation was relatively unaffected. SUC oxidation was also observed in sonicated mitochondria and was unaffected by CHL, suggesting that transport was the limiting factor in SUC oxidation. Measurement of SUC accumulation in mitochondria showed transport to be reduced 75-84% in the presence of CHL (500 μ g/ml). Studies in the presence of phthalonate indicated that succinate is primarily transported by the AKG carrier in the heart. CHL also inhibited mitochondrial AKG release in the presence of MAL and GLU indicating impairment of the malate/aspartate shuttle by CHL. Impairment of the malate/aspartate shuttle resulting from inhibition of the AKG carrier may contribute to the acute clinical toxicity of CHL.

1240 USE OF P-31 NMR IN DIAGNOSIS AND THERAPY OF A FAMILIAL CARDIOMYOPATHY. Glenn Whitman, Britton Chance, B.J. Clark, Richard Kelley, John Maris, Aldan Harken, Hans Bode. The Medical School of the University of Pennsylvania, Philadelphia and Harvard Medical School, Boston.

An 8 mo old female with a familial congenital hypertrophic cardiomyopathy and cardiomegaly showed a chronic hyperchloremic acidosis, nonketotic fasting hypoglycemia, normal ketogenesis from medium chain triglycerides, but evidence of an abnormal redox state. Serum and muscle carnitine content were low normal, 5 mo carnitine therapy had failed to halt disease progression. Muscle carnitine transferase activity was elevated. To determine 1) if in vivo P-31 NMR spectroscopy could detect a metabolic abnormality in human myocardium, and 2) if P-31 NMR could be used to evaluate therapy designed to improve myocardial energy production, measurements were made using a TMR-32 Oxford Research Systems magnet (30 cm bore, 1.9 Tesla) with a 5 cm surface coil positioned over the sternum. This demonstrated an abnormally low phosphocreatine/inorganic phosphate ratio (PCr/P_i) compared to control (1.0±0.05 vs 2.0±0.3, R<0.01). PCr/P_i remained low in the fasting state with or without administered MCT oil, but improved substantially following I.V. glucose or a carbohydrate enriched meal (PCr/P_i = 1.8±0.1, not different from control). We conclude that P-31 NMR can be used to evaluate the high energy phosphate profile of the human heart. Furthermore, when used in conjunction with dietary manipulations, it can be used to optimize therapeutic interventions, as shown in redox manipulations in another female who had skeletal muscle cytochrome-b deficiency. (Biophys. Jour., Feb. 1984 abstract)

1241 ONTOGENIC REGULATION OF PHOSPHORYLASE KINASE (PK) IN RAT LUNG. J.A. Whitsett, E. Feltner, W. Hull. Children's Hospital, Univ. of Cincinnati

Pulmonary glycogen serves as substrate for surfactant lipid synthesis by Type II cells during the perinatal period. Glycogen is depleted from these cells in association with activation of phosphorylase (phos b). Phos b is phosphorylated to phos a by phosphorylase kinase (PK). The present study tests the hypothesis that known depletion of pulmonary glycogen is associated with ontogenic changes in PK. Lung PK was quantitated by phosphorylation of endogenous and exogenous phos b assessed by SDS-PAGE and autoradiography. ³²P-Phos a was the major Ca²⁺-dep phospho-protein in fetal lung cytosol by 2-D, IEF-PAGE, co-migrating with purified muscle enzyme. PK increased from day 17 to 20-21 gestation declining to undetectable levels within a week of age. PK was Ca²⁺-dependent, EC₅₀ Ca²⁺ 10⁻⁷M. Exogenous phos b was readily phosphorylated by fetal but not adult cytosol. Added purified exogenous PK did not enhance ³²P-phos a in postnatal lung. PK was also demonstrated in purified Type II cells from rat. Activity was highest 16 hrs after isolation, decreasing during culture 3-4d. Conclusion: phosphorylase kinase activity was identified in cytosol from both Type II cells and fetal lung. PK increases prior to birth and decreases dramatically postnatally. Decreases in both phos b (substrate) and phosphorylase kinase may account for known postnatal decreases in phos a activity. High PK activity is associated with glycogen depletion and surfactant synthesis in the Type II cells at 20-21d gestation in the rat.