997 THE MEASUREMENT OF 5' ADENOSYLCOBALAMIN IN SERUM MAY PROVIDE A RAPID METHOD OF DETERMINING THE CAUSE OF METHYLMALONIC ACIDEMIA. Salvador Castells, Sheldon P. Rothenberg, Kenneth Rebong, Edward Quadros, Wayne A. Fenton, and Leon E. Rosenberg. Depts of Peds. & Med., SUNY/H.S.C., VA Hosp, Bklyn, N.Y. & Dept. of Human Genetics, Yale Univ. School of Med. New Haven, Conn.

Methylmalonic acidemia (MMA) is either due to a deficiency or a defective form of methylmalonyl-CoA mutase, or from deficient formation of the cobalamin (Cbl) cofactor for this enzyme, 5' deoxyadenosylcobalamin (ado-Cbl). It is important to establish the cause early because defective synthesis of ado-Cbl can respond to treatment with hydroxo-Cbl. A therapeutic trial with hydroxo-Cbl and analysis of fibroblast cultures for the mutase enzyme has been used to distinguish these forms. A 6 week old female was found to have MMA after presenting with vomiting and dehydration. Initial treatment included hydroxo-Cbl with protein restriction and the infant improved. Fibroblast cultures by genetic complementation indicated that the infant has an abnormality of methylmalonyl CoA mutase of mut class of mutations, generally unresponsive to hydroxo-Cbl. A specific RIA for ado-Cbl has become available and the serum concentration of this cofactor was 400pg/ml (normal 60-120pg/ml), while the infant was receiving hydroxo-Cbl indicating that there was no impairment in the synthesis of ado-Cbl. Thus, this provided additional evidence to the genetic complementation studies that established the defect in this infant to rest with the enzyme, methylmalonyl CoA mutase. The improvement continued after withdrawal of hydroxo-Cbl indicating that the initial response was due to the dietary restriction of protein.

●998 FATAL CARDIOMYOPATHY IN CYTOCHROME OXIDASE DEFICIENCY: LIGHT MICROSCOPIC, HISTOCHEMICAL, BIOCHEMICAL AND ELECTRONMICROSCOPIC STUDY C.H. Chang, R. Poland, B.H. Robinson and S. DiMauro. Wayne State Univ Sch of Med, Children's Hospital of Michigan, Dept of Peds, Detroit, Mich and Columbia University, The Hospital for Sick Children, Dept of Peds, New York, NY.

A black male and a white female neonate presented with respiratory distress, profound metabolic acidosis and progressive cardiac failure. Cytochrome oxidase deficiency was demonstrated in skeletal muscles in both cases. Both babies were treated with L-carnitine without response and died after 18 days. On postmortem examination, hypertrophic cardiomyopathy was found to be the main cause of their demise. Histologic brain studies showed focal gliosis and lesions suggestive of Leigh's disease were absent. Light and electron microscopic examinations, histochemical and biochemical studies were performed on cardiac muscle and skeletal muscles in both cases, and mitochondrial enzyme profile on fibroblast culture in one case. Fatal cardiomyopathy occurring in infancy is known to be associated with several metabolic disorders, notably Pompe's disease and system carnitine deficiency. Cardiomyopathy associated with cytochrome oxidase deficiency, a recently described mitochondrial disorder associated with early death in infancy, has not been described. Cytochrome oxidase deficiency needs to be included in the increasing list of causes of cardiomyopathy, especially those occurring in early childhood.

999 DIABETES AND OCULAR AND RENAL COMPLICATIONS: H. Peter Chase, William E. Jackson, Sandy Hoops, Sieglinde Freed, Rebecca S. Cockerham, and Donough O'Brien. Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Department of Pediatrics, Denver, Colorado.

This study was designed to assess the relationship between diabetes control (monitored by yearly or more frequent HbA_1 determinations) and the ocular and renal complications of type I diabetes. 149 patients (aged $\geq$ 14 years) with type I diabetes $\geq$ 5 years had microalbumin excretion rates (AER) determined in resting, peak exercise and overnight urine samples. They also had complete eye exams (including fluorescein photography and fluorophotometry). HbA_1 levels were available (normal=6.3 to 8.2) for the previous 3 to 8 years for all subjects.

99 subjects had a normal AER on all 3 urine samples. An elevated AER ($>$ 30 µg/min) was found with exercise in 26 and 24 had elevated levels in all 3 samples. The mean HbA_1 for those with all normal AER was 11.5$\pm$ 1.3 ($\pm$ 1 S.D.) compared to 12.7 $\pm$ 1.5 for those with any elevated AER (t-test: $p<0.0001$).

60 cases had no eye changes and had a mean longitudinal HbA_1 of 11.4 $\pm$ 1.6 compared to 89 subjects with ocular changes who had a mean HbA_1 of 12.2 $\pm$ 1.3 (t-test: $p<0.0008$).

Chi-square analysis showed a significant relationship ($p<0.03$) between the presence of elevated AER and of ocular changes.

This study shows a relationship between longitudinal glucose control during childhood and the ocular and renal alterations of type I diabetes.

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●1000 CHRONIC RENAL DISEASE IN TYPE I GLYCOGEN STORAGE DISEASE, Yuan-Tsong Chen[a], Rosalind A. Coleman[a], Jon I. Scheinman[a] and James B. Sidbury[b], [a]Duke Univ. Medical Center, Dept. of Pediatrics, Durham, NC; [b]Natl. Inst. of Child Health and Human Devl., Human Genetics Branch, Bethesda, MD

Clinical manifestations of type I glycogen storage disease (GSD-I) include growth retardation, hepatomegaly, lactic acidosis, hyperuricemia and hyperlipidemia. Kidney enlargement is common, but renal disease has not been appreciated as a major component of GSD-I. Of thirty-four GSD-I patients (32 type Ia and 2 type Ib) under our care, 15 children less than 10 years old have normal renal function. Of the 19 older patients (11 to 47 y), 11 have evidence of disturbed renal function, manifested by proteinuria, hypertension or decreased creatinine clearance, and three patients have died with renal failure (18, 24 and 28 y). Hyperuricemia had been well-controlled with allopurinol and diet. Only three female patients have had recurrent urinary tract infections. We investigated two patients (13 and 18 y) with progressive deterioration of renal function after a long history of proteinuria. Albuminuria of up to 5 g/day was documented. Renal biopsy showed focal segmental glomerulosclerosis and interstitial fibrosis. Neither patient had evident renal tubular dysfunction or urological abnormalities. Progressive renal dysfunction appears to be a frequent and serious potential complication of GSD-I. Its relationship to glucose-6-phosphatase deficiency in the kidney itself, to the lack of effective dietary management of hypoglycemia, or to recurrent infection is unclear.

●1001 THE EXAGGERATED "DIABETOGENIC STATE" OF PREGNANCY: EXOGENOUS PLACENTAL LACTOGEN (PL) ACCELERATES FETAL GROWTH IN THE RAT. James W. Collins Jr., Sandra L. Finley, Daniel Merrick, Edward S. Ogata. Northwestern Univ. Med. School, Depts., of Peds., Ob/Gyn, Chicago.

As pregnancy progresses, "diabetogenic" factors develop in the mother which enhance metabolic fuel availability to the fetus. PL is one of these. The effect of increasing PL upon maternal and fetal metabolism is unknown. We implanted osmotic minipumps loaded with human PL (providing 75 ug PL/24 hr). This doubled PL conc. By day 18, PL fetuses were significantly heavier (2.58$\pm$.04 v 2.15$\pm$.07g, $p<.01$) and had larger placentas (.816$\pm$.02 v .578$\pm$.03g, $p<.001$) than controls (C). This resulted in part from enhanced maternal fuel availability since fetal plasma glucose (50.8$\pm$3.8 v 33.2$\pm$4.3 mg/dl, $p<.001$) and insulin (126.8$\pm$19.6 v 79.2$\pm$7.1 uU/ml) were elevated while fetal/maternal glucose ratios did not differ between PL and C. Of note, from day 18 to term, the liver/body ratio was significantly diminished in PL. On these days, plasma conc. of glucose, insulin, and glucagon did not differ between PL and C fetuses. At birth, PL pups were heavier than C (5.62$\pm$.04 v 5.37$\pm$.06, $p<.001$) and demonstrated the normal surge in plasma glucose (68.2$\pm$4.6$\rightarrow$95.7$\pm$10.3 mg/dl) and decrease in insulin (97.2$\pm$18.0$\rightarrow$27.3$\pm$17.5 uU/ml). Plasma glucagon conc was normal. Exogenous PL enhances fuel availability to the fetus and accelerates growth. While this may be mediated by insulin, a growth stimulating hormone, the relatively limited hepatic growth in PL suggests mechanisms other than insulin for growth stimulation.

▲1002 **EFFECT OF INCREASING GLUCOSE CONCENTRATION ALONE ON FETAL GLUCOSE UTILIZATION.** Jane E. DiGiacomo, William W. Hay Jr. and Frederick C. Battaglia, Div. of Perinatal Medicine, University of Colorado School of Medicine, Denver, CO 80262

Fetal utilization of glucose is related to fetal glucose concentration[G], but previous studies did not separate the effects of ↑[G] and the accompanying increase in insulin[I]. To study the effects of ↑[G] alone on fetal glucose metabolism, we infused U-^{14}C-glucose, antipyrine (to measure umbilical blood flow, UBF), and somatostatin[S] (to suppress insulin release) in 7 chronically catheterized late gestation fetal lambs, measuring umbilical O_2 and glucose uptake (UO_2U, UGU) (Fick principle) and fetal glucose utilization and oxidation rates (GUR, GOxR) (tracer methodology) during a control period and after a 3 hr[S] infusion plus 90 minute hyperglycemic clamp.

	[G] mg/dl	[I] uU/ml	UBF ml/min/kg	UO_2U mmol/min/kg	UGU	GIR	GUR	GOxR
					-----mg/min/kg-------			
Control	18.26	19.7	158.5	0.25	4.44	---	4.90	2.65
SD	2.73	7.1	41.1	0.06	1.03	---	1.02	0.48
[S]+↑[G]	42.52	13.5	144.4	0.291	-1.19	6.39	6.86	3.93
SD	5.00	4.3	39.5	0.070	1.21	1.56	1.73	0.88
P-value	<0.01	>0.1	>0.1	>0.1	<0.01	---	<0.02	<0.05

Conclusions: With a 130%↑in [G], GUR increased by 40% and GOxR by 50%. This GUR response is less than the maximal 2-fold increase previously measured in this laboratory with ↑[I] at both euglycemia and ↑[G]. Thus, (1) acute suppression of insulin release reduces the GUR response to hyperglycemia; and (2) at least 2 mechanisms control fetal metabolic response to changes in [G], one [I]-dependent and one [I]-independent.