1230 NONKETOTIC HYPERGLYCINEMIA (NKH): PERHAPS NOT SO RARE - John A Duncan, John S Curran, John I Malone, Ralphael C Foster, Steve A Benford, Lewis A Barness and T A Tedesco, Univ. South Florida Medical Center, Dept. of Pediatrics, Tampa.

Since 1976 four unrelated patients have presented with NKH. Only one was of consanguineous parents. One presented by 8 hours of life, the others within 3 days. Findings included myotonic jerks, lethargy, hypotonia and respiratory failure. Diagnostic laboratory data are:

	SERUM		CSF		URINE	
PATIENT	GLYCINE	SERINE	GLYCINE	SERINE	GLYCINE	SERINE
	(mM)		(mM)		(mM)	
A	1.11	0.14	0.45	0.06	7.4	0.37
B	1.05	0.21	0.56	0.01	5.1	0.47
C	1.69	0.16	0.35	0.05	14.7	0.35
D	1.50	0.07	0.12	0.05	9.7	0.20
CONTROL RANGE	.12-.55	.07-.54	0-.03	0-.08	.07-1.5	.08-0.5

Other organic acid and amino acid metabolites were normal. Sodium benzoate and protein restriction were used in all four patients. Other therapy included strychnine, pyridoxine, phenobarbital and dilantin. Two died before 8 months, one before 2 years, one survives at 6 years with severe psychomotor delay. In order to have diagnosed 4 cases in 7 years in our catchment area we estimate the frequency of NKH to be about 1 in 60,000 births.

●1231 Therapeutic Doses of Valproate (VAL) Affect Liver Glucose, Fat, Amino Acid, Adenylate, Coenzyme-A(CoA) and Carnitine (CARN) Metabolism in Infant Mice. J.H. Thurston, J.E. Carroll, R.E. Hauhart, J.A. Schiro. Washington Un. Dept. Pediat., St. Louis Children's Hospital, St. Louis, MO.

We have reported that chronic VAL administration reduced ketonemia in suckling mice and fasting epileptic children. This study shows that acute VAL has a similar effect. Thirty min after s.c. injection of 4-d-old mice (N=8) with 60 mg/kg of VAL, plasma β-hydroxybutyrate (β-OHB) levels fell 79% (0.197 ± 0.011 mM (mean ± SE) vs 0.952 ± 0.023 in controls), and plasma glucose, 33% (3.95 ± 0.33 mM vs 5.89 ± 0.18). In liver, free CoA levels dropped 67% (22.8 ± 2.5 µmol/kg vs 69.3 ± 4.4), and acetyl-CoA, 73% (7.6 ± 0.7 µmol/kg vs 28.3 ± 2.4) . Liver free CARN decreased 47% (74.5 ± 9.2 µmol/kg vs 140 ± 14). Liver metabolism was inhibited at CoA-requiring steps; pyruvate and α-ketoglutarate levels increased 50%. Citrate and malate levels fell 50%. While liver alanine doubled, levels of aspartate, glutamate and glutamine decreased 40% to 50%. AMP levels fell 34%, but ATP and ADP were unchanged. P values for above differences < 0.001. Since CoA and CARN are essential cofactors in fatty acid oxidation and acetyl-CoA levels control ketogenesis, it is not surprising that VAL reduced plasma β-OHB levels. Glucose and amino acids may be reduced due to their use as metabolic fuels. Gluconeogenesis may also have been inhibited (pyruvate carboxylase is acetyl-CoA dependent). Decreases in aspartate and glutamine support possible decreased AMP synthesis. Findings appear relevant to the hepatotoxicity of VAL in some children and suggest stratagems for prevention and/or treatment.

†1232 DOES A DEFECT IN INSULIN LIKE GROWTH FACTOR-I (IGF-I) GENERATION EXIST IN INSULIN DEPENDENT DIABETES(IDDM)? E. Topper, M. Press, S. Amiel, R. Hintz, M. Genel, J. Gertner and W. Tamborlane. Yale and Stanford Medical Schools.

Elevated, normal and low IGF-I values have been reported in IDDM. To clarify the influence of blood glucose (BG) control on IGF-I in the young diabetic, we studied 19 IDDM (16±1yrs) before and after one week of intensified Rx. During conventional Rx, IGF-I levels were markedly reduced in comparison to age-matched healthy controls (198±20 vs. 448±34 ng/ml, p<0.001) and were negatively correlated with glycosylated Hb values (r=-0.55, p<0.02). Insulin infusion pump Rx, which lowered mean 24hr BG from 233±16 to 110±5 mg/dl, induced a rise in IGF-I (198±20 to 252±34 ng/ml, p<0.005) despite a 30% fall in mean 24hr growth hormone (GH) levels, (p<0.05). To evaluate this apparent defect in IGF-I generation, we administered exogenous GH (0.1U/kg IM x 4 days) to 8 prepubertal IDDM (11.4±0.3yrs) maintained on their usual Rx, and to 7 age-matched healthy controls. Despite a significant rise in BG from 176±21 to 276±22 mg/dl(p<0.001), exogenous GH resulted in a marked increase in IGF-I (from 63±11 to 146±27 ng/mg, p<0.02) indistinguishable from that observed in non-diabetic children (58±7 to 112±24 ng/ml).

Conclusions: (1) Poorly controlled IDDM is associated with reduced IGF-I levels which can be restored by improved metabolic control. (2) This defect can be overcome by exogenous GH even in the face of poor metabolic control. (3) Low IGF-I values in IDDM in the presence of high GH levels may be due to reduced biological activity of endogenous GH.

1233 OSTEOCALCIN AND CALCIUM RESPONSE TO INTRAVENOUS 1,25 DIHYDROXYVITAMIN D_3 (IVD) Winston Koo, Jim Poser, Jean J. Steichen, Donna Buckley, Reginald C. Tsang, U. of Cincinnati and Proctor & Gamble, Cincinnati

Osteocalcin (OC) is the major non-collagenous bone protein, has Ca binding properties and is involved in bone mineralization; elevated serum levels occur with high bone turnover and after $1,25(OH)_2$ vit D. Its role in infancy is unknown. In a pilot, uncontrolled study, we found oral $1,25(OH)_2$ D_3 did not raise serum Ca in <1500g (VLBW) infants at graduated doses up to 3 mcg/kg/d. In a controlled study, we tested the thesis that high dose IVD elevates serum Ca and OC in VLBW infants. 22 preterm, wt appropriate infants (750-1500g) were matched in 250g ranges and randomly assigned to IVD 4 mcg/kg/d x 3 d from 1st d of life vs controls. Gestation and Apgars were comparable for grps. Serum OC (RIA specific for humans N 4-9 ng/ml, term 4-110, mean 41) rose from 19±6 ng/ml (mean±SEM) to 96 at 34 hr, 122 at 58 hr and 154 at 80 hr ($p<.05$ ANOVA vs d 1) in IVD but was unchanged in controls. Serum Ca rose from 7.3± 0.24 mg/dl to 7.8, 8.5 ($p<.005$) and 9.2 ($p<.05$) at corresponding times in IVD, but was unchanged in controls, 7.2, 6.6, 7.1 until last point 9.3 ($p<.05$). Serum Mg but not serum P increased with age; both were unaffected by IVD. Ca correlated with ionized Ca ($r=0.89$, $p<.001$). Furthermore OC correlated with Ca and ionized Ca ($r>0.46$, $p<.04$). Thus there is a late response of serum Ca and OC to high 1,25(OH)D doses, supporting the thesis that osteocalcin may be responsive to $1,25$ $(OH)_2D$ in VLBW infants. We speculate that bone turnover, as reflected by osteocalcin elevations, is involved in the elevation of serum Ca from $1,25(OH)_2D$ in infancy.

1234 THE EFFECTS OF PROSPECTIVE EARLY STRICT MANAGEMENT OF MATERNAL DIABETES ON MATERNAL IONIZED CALCIUM & $1,25(OH)_2$ VITAMIN D, Philip Shaul, Jean Steichen, Donna Buckley, Kay Ellis, Reginald C. Tsang, University of Cincinnati.

Chemically induced murine diabetes is associated with negative calcium (Ca) balance & decreased serum 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels; insulin therapy corrects these defects. We hypothesized that diabetes in pregnancy causes decreased maternal ionized Ca (Cai) & $1,25(OH)_2D$, with indirect effects on neonatal Ca, & that prospective strict management of diabetes from early pregnancy ameliorates these changes. In a comprehensive clinical trial, 57 pregnant insulin-dependent diabetics were randomly assigned during the first trimester to strict vs customary management (Sm vs. Cm) grps. Maternal Cai at delivery was higher in Sm (4.52 ± 0.08 SEM mg/dl) vs. Cm (4.27 ± 0.07 mg/dl, $p < 0.02$). There was no difference between grps. in maternal 25-hydroxyvit. D (25OHD) or $1,25(OH)_2D$ at delivery. Infants (IDMs) in Sm grp. had higher 24 hr. serum Ca (8.3 ± 0.20 mg/dl) vs. Cm grp IDMs (7.8 ± 0.23 mg/dl, $p < 0.04$), but no difference was noted by 72 hr. There was no difference in Sm vs. Cm neonatal 25OHD (27 ± 2.9 ng/ml vs. 27 ± 3.1) or $1,25(OH)_2D$ (60 ± 9.4 pg/ml vs. 60 ± 6.9) at 24 hrs. Hypocalcemic (Ca < 7.0 mg/dl) (HC) IDMs had lower maternal Cai (4.15 ± 0.09 mg/dl) vs. nomocalcemic (NC) IDMs (4.46 ± 0.06, $p < 0.02$); there was no difference in maternal or neonatal 25OHD & $1,25(OH)_2$ for HC vs. NC infants. Thus, strict management of maternal diabetes results in increased maternal Cai, but has no effect on maternal $1,25(OH)_2$. We speculate that improved Ca status in the diabetic pregnancy contributes to improved neonatal Ca homeostasis.

1235 ADENOSINE TRIPHOSPHATE (ATP) AND RED BLOOD CELL (RBC) GLYCOLYTIC INTERMEDIATES IN PRETERM INFANTS ON THE FIRST DAY OF LIFE. Susan F. Travis, Linda M. Sacks,* Savitri P. Kumar,* and Maria Delivoria-Papadopoulos. Jefferson Med. Coll., Dept. of Pediat., Cardeza Fnd. for Hem. Res., and Univ. of PA Depts. of Pediat. & Physiol., Phila., PA.

RBC glycolytic intermediates and ATP were evaluated on the first day of life in 47 appropriate for gestational age preterm infants divided into 3 groups, 28-30 wks, 31-33 wks, and 34-36 wks, and compared to prior results in term infants. Mean concentrations of glucose-6-P (G-6-P), triose P (TTP), and ATP were significantly higher than in term infants (G-6-P: 77.3±11.4 vs 53.3±8.6; TTP: 27.7±10.8 vs 19.2±6.9; ATP: 1365±220 vs 1056±144 nmoles/ml RBC, respectively), but were appropriately elevated for the young mean age of the RBC population (G-6-P: 66.5±23.1; TTP: 22.9±5.3; ATP: 1320±231). The concentration of RBC 2,3-DPG was significantly decreased when compared to term infants (4691±383 nmoles/ml RBC) and was lowest at 28-30 wks (3567±618). An increase in 3-phosphoglycerate was noted in preterm infants and was inappropriately elevated for RBC age at 28-30 wks (68.0±10.2 vs 55.5±7.5 nmoles/ml RBC in young RBC's). This pattern of glycolytic intermediates suggests a young RBC population metabolizing at increased glycolytic rate with increased flow through the phosphoglycerate kinase reaction rather than the 2,3-DPG bypass in "normal" preterm infants. In 2 infants 28-30 wks with low intracellular pH (6.866; 7.010), there was a marked decrease in 2,3-DPG (2281; 1882 nmoles/ml RBC), ATP (650; 750 nmoles/ml RBC), and all intermediates distal to the phosphofructokinase (PFK) step, indicating a crossover at PFK secondary to acidosis. These studies show normal preterm infants have RBC's that are at a metabolic disadvantage that increases with hypoxia and/or acidosis.