1123 COPPER LOADING (CuL) STUDIES IN BRINDLED (Br) MOUSE HEMIZYGOTES AND HETEROZYGOTES. A. Garnica, S.M.T. Chang, Dept. of Pediatrics, U. of Fla. College of Medicine, Gainesville, Fla.

The X-linked mouse mutant Br with defective Cu metabolism is a model for Menkes Kinky Hair Syndrome (MKHS). Female heterozygotes have abnormal Cu metabolism but no neurologic symptoms. Baseline Cu in newborn Br males demonstrate Cu in brain and liver lower than nl newborns/adults and adult Br females; kidney Cu is higher than nl newborns/adults. In the wk-old Br female, liver Cu is low and kidney Cu higher than nl. Brain and liver Cu in adult Br females is comparable to nl adults; kidney Cu is comparable to Br male and approx 5x the nl adults/newborns. CuL was conducted in 6-10 day old mice. After CuL, brain and liver Cu of hemizygotes remained lower than nl. Liver Cu in nl remained approx 6x that of Br males, while kidney Cu was approx 1/3 that of Br males. Adult mice of approx 20 gm received Cu 35 mcg/kg/d S.C.x20d. Before Rx Cu levels in kidney of Br females were higher than non-Rx nl; brain and liver Cu were no different from nl. After CuL, Cu in all tissues studied increased in nl and heterozygotes. However, CuL Br females accumulated kidney Cu approx 8x CuL nl controls. Br females have normal brain Cu; however, their low newborn liver Cu and persistent high kidney Cu are similar to male Br hemizygotes. CuL Br females results in increased liver and kidney Cu. Our data implies that defective liver and kidney Cu metabolism in Br females has no clinical effect. Only defective brain Cu metabolism, as in Br male, apparently is clinically important.

1124 PERINATAL COPPER (Cu) TREATMENT (Rx) IN BRINDLED (Br) MICE. A. Garnica, S.M.T. Chang, Dept. of Pediatrics, U. of Fla. College of Medicine, Gainesville, Fla.

X-linked murine mutant Br is a model for Menkes Kinky Hair Synd., a disorder of Cu metabolism with no effective post-natal Rx. To assess response to prenatal Rx, pregnant dams received Cu, 35 mcg/kg/d S.C., last 1-15d of pregnancy. This resulted in reduced litter size and decreased viability of newborn mice. Prenatal Cu-Rx also did not increase affect tissue Cu.

Normal (nl) mice born to nl and Br heterozygote mothers were sacrificed immediately after birth and brain, liver, kidney and placental Cu determined for comparison with values in Br male hemizygotes. The brain and liver Cu in Br males was lower than nl; the kidney Cu was higher than nl; the placental Cu was approximately twice nl. No differences were found in the Cu contents of nl mice born to nl vs. carriers. The 1st wk of life, wgt increased in nl 3-5xb.w. vs. 2-3xb.w. in the Br males. Brain Cu content in nl remains stable, while brain Cu in Br males decreased to approx. 1/4 nl. Neither wgt gain nor brain, liver, kidney Cu at the end of 1st wk of life were altered by prenatal Rx; only placental Cu increased. Offspring of mothers Cu-Rx during pregnancy were then Cu-loaded at age 7d: brain, liver and kidney Cu did not increase in nl; liver Cu in Br males increased slightly, not to levels comparable to age-matched nl, but kidney Cu increased significantly. From these data we conclude that response to Cu-Rx in the young Br male is analagous to that of the infant with Menkes Synd. In addition, prenatal Rx is not effective and may be harmful.

1125 DELAY IN DEGRADATION OF PULMONARY GLYCOGEN IN FETUSES OF STREPTOZOTOCIN-DIABETIC RATS. Ira H. Gewolb, Carolyn Barrett, Jacob J. Greenberg, Joseph B. Warshaw, Yale Univ. Sch. of Med., Dept. of Ped., New Haven, CT.

Pulmonary glycogen is thought to provide carbohydrate precursors for the synthesis of surface active phospholipids. Since the infant of the diabetic pregnancy (IDP) has delayed pulmonary maturation, we studied the developmental profile of lung glycogen in rat IDP from day 16 to term (day 22). Diabetes was induced by injection of 40 mg/kg of streptozotocin. Controls and IDPs had equal lung glycogen concentrations between day 16-20; however, the normal pattern of glycogen breakdown during the final 2 days of gestation was blunted in the IDPs.

Day	16	18	19	20	21	22
IDP -±SE	64 ± 10	143 ± 33	200 ± 20	264 ± 25	257 ± 17	162 ± 22
Control -±SE	54 ± 15	162 ± 6	214 ± 7	256 ± 11	190 ± 14	88 ± 7
P =	NS	NS	NS	NS	<.01	<.01

Glycogen synthetase levels were similar in IDPs and controls. Glycogen phosphorylase (total and active fractions) in the IDPs did not differ from controls. However, the ratio of active/total phosphorylase in the last 3 days of gestation, the time of rapid glycogen breakdown, was significantly lower in the IDPs (.17 ± .02 vs. .24 ± .01, p <.005).

Preliminary analysis of lung phospholipids in the IDPs indicate a maturational delay by days 21-22, but not for day 20. The increased lung glycogen stores and the decreased lung phospholipid levels late in pregnancy suggest that substrate unavailability may be related to the delay in lung maturation in IDPs.

● **1126** AN IMBALANCE IN PLATELET-VASCULAR PROSTAGLANDIN SYNTHESIS INDUCED BY HOMOCYSTEINE (HC) AND HOMOCYSTEIC ACID (HCA). Janet E. Graeber, Marie J.Stuart, Jeffrey Slott, Rodney E. Ulane, and Joseph D. Schulman, NICHD, NIH, Bethesda and SUNY, Dept. of Peds., Syracuse, New York.

Homocystinuria is characterized by serious vascular thromboses and elevated plasma levels of HC and HCA. The etiology of the thromboses is unknown. Platelets (plts) produce proaggregatory and prothrombotic Thromboxane A_2 (TXA_2) while vascular endothelium produces antiaggregatory and antithrombotic PGI_2. An imbalance in production of TXA_2 and/or PGI_2 can lead to bleeding or thrombosis. We investigated production of plt TXB_2 (the end product of TXA_2) and vascular 6-Keto-$PGF_{1\alpha}$ (the end product of PGI_2) in plts and vascular endothelium exposed in vitro to HC and HCA, 0.4 to 2.0 mM. Conversion of ^{14}C arachidonic acid (AA) to plt TXB_2 was increased in the presence of HC or HCA. In 8 paired experiments, mean plt TXB_2 increased to 19.4±3.5% (1SE) in the presence of HCA, compared to control values of 14.6±3.6% ($p<0.01$). Similarly, in 4 paired experiments plt TXB_2 was increased (18.7±2.3%) in the presence of H.C., when compared to a mean value of 7.8±1.1% ($p<0.05$) in the control plts. No differences in 6-Keto-$PGF_{1\alpha}$ production were observed in 6 paired experiments when vessels were incubated with either buffer, HC or HCA (0.73±.07; 0.7±.05; 0.76±.07%). These studies demonstrate that HC and HCA alter plt and vascular AA metabolism by increasing production of prothrombotic plt TXA_2 without a compensatory increase in antithrombotic vascular PGI_2. Such an imbalance may explain the marked thrombotic tendency in Homocystinuria.

1127 SODIUM BENZOATE IN THE TREATMENT OF HYPERAMMONEMIA IN NEWBORNS. Thomas P. Green, (Spon. by B.L. Mirkin)Div. Clin. Pharm., U. Minn. Med. School, Minneapolis 55455.

Benzoate is effective in increasing the excretion of urinary nitrogen in patients with hyperammonemia. In jaundiced newborns, however, the potential exists for benzoate, if present at high serum concentrations, to displace bilirubin from albumin binding sites and thereby increase the risk of bilirubin toxicity. This risk was evaluated by studying the disposition of benzoate in 3 non-jaundiced newborns with severe hyperammonemia.

The infants received sodium benzoate (125mg/kg i.v. q6h). Benzoate was efficiently converted to hippurate (metabolic clearance was 1.89-2.37 ml/min), whereas the urinary elimination of unchanged benzoate was minimal (clearance 0.04-0.10 ml/min). Hippurate was eliminated primarily by renal excretion. Quantitation of benzoate and hippurate in the urine and peritoneal dialysis fluid at steady state accounted for 70-120% of the administered benzoate dose. Steady state serum concentrations of benzoate ranged from 231-517 mg/L, however the onset of renal failure in one patient led to benzoate levels exceeding 1000 mg/L despite the absence of glycine depletion. These serum concentrations, based on the known affinity constants of benzoate and bilirubin for albumin would increase the unbound fraction of bilirubin by 2 to 12 fold.

Further use of this drug in newborns should be carried out with monitoring of benzoate and hippurate concentrations so that potentially toxic serum concentrations can be avoided and safe effective dosage regimens for this age group can be devised.

1128 BREAST MILK RELATED "PHYSIOLOGIC HYPERCALCEMIA AND HYPERMAGNESEMIA" WITHOUT CHANGES IN CALCIOTROPIC HORMONES F.R. Greer, R.C. Tsang, J.J. Steichen, U. of Cincinnati, Ohio

Simultaneous Ca, Mg, P and calciotropic hormone levels have not been reported prospectively in sera of breast fed infants and their mothers and in relation to breast milk minerals. Eighteen lactating mothers and their exclusively breast fed term infants were followed for 6 mos. Breast milk Ca and Mg did not change, but P was decreased by 6 wks (14.7±0.6 vs 12.7±0.4mg/dl, p<.02) and to 10.7±0.4mg/dl by 6 mos (p<.001). Changes in breast milk minerals did not reflect changes in maternal serum. Maternal serum Ca and Mg increased from 8.6±0.2 to 9.6±0.3 mg/dl (p<.005) and 1.95±.06 to 2.15±.07mg/dl (p<.05); P was unchanged. However, as breast milk P decreased, infant serum P also decreased from 7.9±0.4 to 5.7±0.1mg/dl (p<.001) by 6 mos. By linear regression, infant P vs breast milk P, r=0.388, p<.01. As infant serum P fell, Ca and Mg increased from 9.2±0.3 to 10.4±0.3mg/dl (p<.005) and 1.92±0.07 to 2.47±0.08mg/dl (p<.001), respectively. Serum Ca and Mg at 6 mos were elevated vs adults (Ca 9.7±0.07 and Mg 2.19±0.02 mg/dl, p<0.01). Infant serum parathyroid hormone and calcitonin remained unchanged and did not correlate with serum Ca, Mg or P. Thus breast milk Ca, Mg and P do not reflect maternal serum minerals; infant serum P decreases with decrease in breast milk P; relative hypercalcemia and hypermagnesemia occur in breast fed infants at age 6 mos unrelated to changes in calciotropic hormones; we speculate that the Ca and Mg changes are related to decreasing P in breast milk.