1249 CELLULAR METABOLISM OF LEAD: A KINETIC ANALYSIS IN CULTURED OSTEOCLASTIC BONE CELLS. John F. Rosen and Joel G. Pounds. Albert Einstein College of Medicine, Montefiore Medical Center, Dept. of Pediatrics, Bronx, NY and National Center for Toxicological Research, Jefferson, AR.

Detailed characterization of the modulation of lead metabolism in bone is necessary to understand the role of skeletal lead in the expression of clinical and biochemical effects of lead. The metabolism of lead in osseous tissue is also important clinically because it is the major site of chelation by therapeutic agents, such as $CaNa_2EDTA$ and d-penicillamine. Experiments were conducted to characterize the steady-state kinetic distribution and behavior of ^{210}Pb and to identify the biological structures or functions associated with the kinetic pools. Bone cells, derived from mouse calvaria, were enriched for osteoclasts by a sequential collagenase digestion and maintained in primary culture for 1 week. Cultures were labeled with ^{210}Pb as 5 μM lead acetate for 20 hr and the kinetic parameters were obtained by analysis of ^{210}Pb washout curves. Cellular metabolism was defined by three kinetic pools of intracellular lead containing ∿10% (S_1), ∿15% (S_2) and ∿75% (S_3) of total cellular lead (1.7-2.2 nmol/mg cell protein). The halftimes for isotopic exchange were 1, 40 and 1000 minutes, respectively. Less than one half of S_1 was labile to chelation by EGTA and thus defined as extracellular. KCN, DNP and DBcAMP decreased S_3, whereas increasing medium PO_4 to 4 mM increased S_3, thereby suggesting that S_3 includes mitochondrial ^{210}Pb. These data indicate that lead is readily mobilized from osteoclastic bone cells and, like soft tissues (hepatocytes), the bulk of cellular lead is associated with mitochondria.

●1250 CEREBRAL CARBOHYDRATE METABOLISM IN POLYCYTHEMIC LAMBS. Ted S. Rosenkrantz and Anthony F. Philipps, Univ. of Conn. Health Ctr., Dept. of Pediatrics, Farmington, CT. (Sponsored by John R. Raye).

Infants with polycythemia are known to have reduced cerebral blood flow (CBF). To determine if this flow reduction is associated with abnormalities in cerebral oxygen and carbohydrate metabolism, we studied eight newborn lambs during a control period and at 60, 180 and 300 minutes after exchange transfusion (ET) with newborn packed red blood cells. Hematocrit (HCT) oxygen content (CaO_2), glucose (G), insulin (I), lactate (L) and pyruvate (P) were measured in arterial (A) and sagital sinus (V) blood. CBF was measured by microsphere technique. Cerebral substrate uptake (Q) or production (-Q) = [A-V] x CBF. 60 min post ET, HCT and CaO_2 rose while CBF and G delivery (D) fell.* At 180 min A [G] fell resulting in a further decrease in GD.* This resulted in a lowered QG ($p = .06$) and G/O_2.+ At 300 min a small rise in CBF led to a small increase in GD and return of QG and G/O_2 to control levels. [I], -QL, -QP were stable throughout the study.

PERIOD	HCT(%)	CaO_2(vol%)	G(mg%)	CBF&	QO_2&	QG@	G/O_2
C	27±5*	14.3±1.9*	103±23	100±14*	7.1±1.2	10.0±3.3	1.09±.44
60	51±9*	24.6±3.2*	97±19	57±16*	7.2±2.2	11.4±6.1	1.09±.46+
180	48±6*	23.4±2.5*	73±14*	67±19*	7.8±2.3	7.7±2.8	.72±.29
300	46±5	22.1±2.0	72±17+	81±24	8.1±2.6	8.7±5.6	.90±.41

M±SD *p<.01, +p<.05 vs C; &(cc·100gm^{-1}·min^{-1}), @(mg·100gm^{-1}·min^{-1})

We conclude that in the neonatal lamb a polycythemia-induced fall in G and CBF effected a significant depression in G delivery and QG.

1251 Effects of Succinylacetone (SA) on Alpha-Methyl-D-Glucoside (AMG) Uptake by the Rat Renal Tubule. Karl S. Roth, Patricia D. Spencer, Edwin S. Higgins, Robert F. Spencer, Medical College of Virginia, Depts. of Pediatrics and Anatomy, Richmond, VA.

Hereditary tyrosinemia is an autosomal recessive disease resulting in hepatorenal dysfunction. The renal manifestations of the disease include renal tubular acidosis of the proximal variety, aminoaciduria, glycosuria and phosphaturia comprising the entity known as the Fanconi syndrome. Individuals with this disease excrete large amounts of succinylacetone, a catabolic end-product of tyrosine, in their urine. We have examined *in vitro* the renal tubular transport interactions of SA with the D-glucose transport analogue, AMG in rat renal tubules.

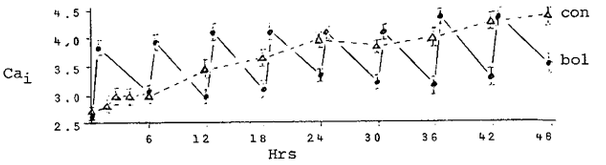
AMG uptake by the rat renal tubule was markedly inhibited by 4 mM SA *in vitro*. The effect was immediate in onset, was primarily on substrate entry and was reflected by a 50% decrease in oxygen consumption. On the other hand, 4 mM SA caused no fine structural alterations in mitochondria or brush border membrane. The inhibition of AMG uptake could be reversed by removing SA from the medium, and was non-competitive in nature. These data are consistent with the hypothesis that SA or succinylacetoacetate from which it is derived may be causally related to the Fanconi syndrome in hereditary tyrosinemia. It is concluded that the use of SA for *in vitro* study of renal tubular transport dysfunction may provide a physiologic model for investigation of the human Fanconi syndrome.

●1252 NATURAL HISTORY AND DIAGNOSTIC DELAY IN PARTIAL ORNITHINE TRANSCARBAMYLASE DEFICIENCY (POTCD). Peter C. Rowe, Stephen L. Newman, Mark L. Batshaw, and Saul W. Brusilow, Dept. of Peds. and Kennedy Inst., Johns Hopkins Med. Inst., Balto., and Wright State School of Med., Dayton.

The natural history of 13 females with POTCD was reviewed. Patients presented as early as 1 week or as late as 6 years. The most common symptoms before diagnosis were non-specific: extreme irritability (100%), recurrent vomiting and lethargy (100%), protein avoidance (92%), ataxia (75%), stage II coma (46%), failure to thrive (46%), and seizures (31%). The median delay between the onset of major symptoms (vomiting and lethargy; seizures; coma) and diagnosis was 16 mos. (range 1-142 mos.). In 38% there was a positive family history. Plasma levels at diagnosis were: NH_4 53-520 uM (NL < 35); AST (median) 83 U/L; ALT (median) 337 U/L; urea, 3-13 mg/dl; citrulline, trace-21 uM (NL: 10-34). Liver OTC activity was 2-55% of normal. Five patients had I.Q. scores < 70 at the time of diagnosis. For those with ≥ 1 episode of stage II coma, the mean I.Q. was 52. Common mis-diagnoses were gastroenteritis, colic, Reye's syndrome, psychogenic cyclical vomiting, and poor maternal-child interactions. Clues to early diagnosis are (1) a positive family history, (2) protein avoidance, (3) recurrent symptoms, (4) response to withdrawal of protein, and (5) onset at the time of weaning from breast milk. Early diagnosis allows prompt recognition and treatment of hyperammonemic episodes, thus reducing the risk of subsequent neurological impairment.

1253 TREATMENT OF EARLY NEONATAL HYPOCALCEMIA. Meir Salameh & Alan R. Fleischman, Albert Einstein College of Medicine, Division of Neonatology, Bronx, N.Y.

Hypocalcemia is a major biochemical abnormality in the first three days of life. This study was designed to define the optimal approach to treatment of this disorder. 12 neonates with ionized calcium levels (Ca_i) <3.0 mg/dl in the first 2 days of life were randomized into two treatment regimens: 7 received bolus infusion over 20 minutes of 125 mg/kg/dose of calcium gluconate Q6H (500 mg/kg/d) and 5 received constant infusion over 24 hours of 500 mg/kg/d. Ca_i was measured serially over the subsequent 48 hours of treatment (mean ± SE):



Both methods were able to maintain Ca_i >3.0 mg/dl. The bolus method resulted in large non-physiologic oscillations in Ca_i while the constant infusion method required several hours to reach physiologic levels but then maintained a constant Ca_i.

We conclude that constant infusion is a more physiologic approach to the treatment of early neonatal hypocalcemia and are presently studying the use of an initial bolus followed by a constant infusion in order to optimize treatment of hypocalcemia.

1254 THE EARLY-ONSET EFFECT OF BILIARY OBSTRUCTION ON CO EXCRETION IN THE RAT. William L. Salomon, Hendrik J. Vreman, Linda K. Kwong, David K. Stevenson. Stanford Univ. Sch. of Med., Dept. of Peds, Stanford, CA

Common bile duct ligation in the adult male Wistar rat increases the rate of total bilirubin formation (TBF) as estimated by the excretion of carbon monoxide (VeCO). This increase is not due to elevation in the hepatic subcomponent of "early-labeled" bilirubin (ELB) formation as measured by ^{14}C-4-Δ-aminolevulinic (J Pediatr Gastroenterol Nutr 3:790, 1984). This study examines total ELB formation in rats 3 days after complete common bile duct ligation. VeCO was measured preoperatively and on the third day after creation of complete biliary obstruction. The rate of ELB formation was measured by recovery of exhaled ^{14}CO following intraperitoneal injection of ^{14}C-2-glycine (20 μCi/100gm) on the third postoperative day. Preoperatively, there was no significant difference in the VeCO between control and experimental rats. On the third postoperative day, the VeCO of control rats had returned to baseline from an elevated rate, due to the surgery, while the VeCO of experimental rats was increased by 31% (paired t-test, $p < 0.02$). Total fractional recovery of injected label over a 36 hr collection period was similar for control ($8.5\pm0.7 \times 10^{-3}$, n=8) and experimental ($8.2\pm0.2 \pm 10^{-3}$, n=7) rats. Based on these data, we conclude that the rise in TBF in this obstructive model is not due to ELB formation. The results further suggest that increased red cell destruction occurs rapidly after short-term biliary obstruction, and may cause the increased TBF, contributing to the pathogenesis of obstructive jaundice.