LEAD INTOXICATION: EVIDENCE FOR A RAPIDLY DISPLACEABLE RED-CELL-LEAD (RBC-Pb) COMPARTMENT. John F. Rosen and Asher Haymovits*. Albert Einstein Col. of Med., Montefiore Hosp. & Med. Ctr., Dept. of Ped., and the Rockefeller Univ., New York

Previous in vitro studies revealed a rapid displacement by ionized calcium (Ca^{++}) of RBC-Pb. This displacement followed a linear dose-response curve above a threshold Ca^{++} concentration of $1\text{mg}\%$. To characterize the specificity of this effect and RBC-Pb compartments, other metals and the fate of Ca^{++} were investigated. RBC s were collected from Pb-intoxicated rats, washed, and incubated for 15 min. at pH 7.40 in a balanced salt solution, to which $\text{Mg}^{++}(2.5\text{mM})$, $\text{Ca}^{++}(2.5\text{mM})$, $\text{Cu}^{++}(1.0\text{mM})$, $\text{Zn}^{++}(1.0\text{mM})$, and La^{3+} (to 2.5mM) were added. Ca^{++} and Pb levels were measured by ion-specific electrode and carbon rod, respectively. La^{3+} , an ion that does not permeate cells, also displaced RBC-Pb according to a linear dose-response curve with a higher affinity compared to Ca^{++} . Cu, Zn, and Mg had little, if any, effect. At pre-incubation RBC-Pb levels ($\mu\text{g}\%$) of $<50, 51-99, 100-180$, the percent decrease in RBC-Pb was negligible, 15.3 ± 1.3 , and 37.8 ± 2.1 , respectively. A distinct stoichiometric relationship was observed in the constant ratio of Ca^{++} medium/RBC-Pb both pre and post incubation.

This rapidly displaceable fraction, above a threshold level of RBC-Pb, is probably membrane bound and accessible for rapid exchange and complex formation with Ca^{++} . This fraction, compared to tightly bound endogenous RBC-Pb, may be the main source of soft tissue Pb and thus of utmost clinical importance. (Supported by the John A. Hartford Foundation, Inc., & PHS AM 11431).

THE SKELETAL METABOLISM OF LEAD: STUDIES OF LEAD TRANSPORT IN BONE ORGAN CULTURE. John F. Rosen and Emma E. Trinidad*, Albert Einstein Col. of Med., Montefiore Hosp., Dept. Ped., New York

Bone is the major storehouse of Pb, and the primary source of Pb mobilized by chelation therapy. To define the metabolism of Pb in bone, Pb transport has been studied in bone organ culture. Pregnant rats were intoxicated with Pb 1 day after breeding. On day #17, $75\mu\text{Ci}$ of Pb^{210} were injected IV; and on day #18, paired fetal bones were planted on grids in BGJ medium, modified to approximate the ionic milieu of the ECF. After 2-3 days, Pb^{210} released into the medium from treated (T) bones was measured by LSC and compared to that released from control (C) bones. Measurements, as T/C medium ratios, were made of the effects of changing the concentrations of calcitonin (CT), parathyroid hormone (PTH), Ca^{++} , PO_4 (P), or Mg^{++} from those in the "normal" (N) medium ($\text{Ca}^{++} 1.4$, P 1.0 , $\text{Mg}^{++} 0.8$, in mM). The results in T/C ($\% \text{p} < .01$, different from 1.0) were: PTH+N: $*2.85 \pm .22$; PTH+2mM P: $*.57 \pm .11$; PTH+4mM P: no release; CT+N: $*.51 \pm .04$; 2.8mM Ca^{++} : $*.81 \pm .08$; PTH+3mM Mg^{++} : $*2.00 \pm .14$. Inhibition by P of PTH action was greater in living than in killed bones, indicating that active resorption was inhibited. Increasing and decreasing concentrations of Ca^{++} and Mg^{++} , respectively, also decreased the efflux of Pb^{210} .

These data represent the first demonstration in vitro that the metabolism of Pb in bone is regulated by CT, PTH, and the ions of the ECF. Future studies in this system are likely to provide biological definition(s) of the real hazards of the skeletal reservoir of Pb. (Supported by the John A. Hartford Foundation, Inc.)

STUDIES ON THE PARADOXICAL EFFECT OF ETHANOL ON LACTATE IN TYPE I GLYCOGENOSIS. A. Sadeghi-Nejad, H. Hochman, A. Binkiewicz and B. Senior. Pediatric Endocrine-Metabolic Service, Tufts-New England Medical Center Hospitals, Boston.

Ethanol, by generating NADH, raises lactate levels in normals but, uniquely and paradoxically, lowers the high lactate of Type I glycogenosis patients. This phenomenon was investigated in 4 patients.

The lactate/pyruvate (L/P) ratios in the patients were high, 30:1 vs. 14:1 in normals. Since the L/P relationship is expressed by the equation $L = P \times K \text{ NADH/NAD}^+$, the L/P ratio, in effect, reflects the NADH/NAD^+ ratio.

Ethanol decreased lactate ($5.3 \pm 0.4 \text{ mM/L}$, mean $\pm$ SEM, to 2.4 ± 0.1 , $\text{p} < .002$), but pyruvate fell even more ($0.18 \pm 0.01 \text{ mM/L}$ to $0.03 \pm .01$, $\text{p} < .005$) thus further raising the L/P ratio (30:1 to 81:1, $\text{p} < .005$). This demonstrated that as in the normal, the oxidation of ethanol had generated NADH. Glucose was unchanged.

The high lactate in Type I glycogenosis derives from hepatic glycogenolysis. Using a constant infusion of 14C lactate, we found that, although glycogenolysis continued, the fall in lactate, after ethanol, reflected decreased formation rather than increased utilization. The increased NADH could cause less lactate to form by diverting carbon flow to the synthesis of triglyceride. Triglyceride did rise.

We conclude that the NADH/NAD^+ ratio may have a critical role in the biochemical abnormalities in this disorder.

A DISORDER RESULTING FROM AN ENZYMATIC DEFECT OF THE RESPIRATORY CHAIN. Boris Senior and Robert L. Jungas. Pediatric Endocrine-Metabolic Service, Tufts-New England Medical Center Hospitals and Dept. of Biological Chemistry, Harvard Medical School, Boston.

Study of two siblings with extreme stunting of growth and severe mental retardation revealed elevated levels of lactate and normal levels of pyruvate, a finding indicative of an increased cytosolic NADH/NAD^+ ratio.

They exhibited striking hypergluconeogenesis from lactate which indicated hepatic involvement.

To determine the cause of the increase of cytosolic NADH, liver tissue was obtained.

The mitochondria failed to utilize B-hydroxybutyrate, glutamate or malate, as judged by oxygen consumption in the presence of ADP. However succinate oxidation proceeded efficiently and exhibited normal respiratory control.

This differential pattern of response established that the increase in cytosolic NADH had resulted from failure of oxidation of intramitochondrial NADH.

We believe this to be the first demonstration in man of an intramitochondrial enzymatic defect involving the respiratory chain.

A NEW SYNDROME OF FAMILIAL PANCREATIC AGENESIS; ESSENTIAL ROLE OF GLUCAGON IN NEONATAL GLUCONEOGENESIS. W.C. Sherwood, G.W. Chance, C.J. Toews, J.M. Martin, E.B. Marliss, Depts. of Ped. and Med., Univ. of Toronto and McMaster Univ., Toronto and Hamilton, Canada. (Intr. by P.R. Swyer)

Two sibs of a consanguineous union showed gross intrauterine growth retardation (IUGR) at term. The first (male, birth wt. 1820g) had ductal pancreatic tissue only and duodenal stenosis at autopsy. The second (female, birth wt. 1280g) developed severe hypoglycemia, but hyperglycemia if glucose was infused $> 7-9 \text{ mg/kg/min}$. Blood lactate (1.5mM) and alanine ($> 800\mu\text{M}$) were raised and FFA ($< 300\mu\text{Eq/L}$) βOH and AcAc ($< 200\mu\text{M}$) were reduced. Glucose disappearance ($\text{Kt} = 0.7\%/min$) was not altered by glycerol (0.6g) or amino acid (1g) infusions. ^{14}C Alanine was not converted to glucose. Plasma HGH was high, cortisol normal, IRI and IRG absent. Glucagon $30\mu\text{g}$ transiently slowed cataglycemia. However with physiologic glucagon infusion ($40\mu\text{g/kg/min}$) glycemia increased, lactate and alanine became normal. At autopsy the vestigial pancreas had neither islets or acini, nor IRI or IRG, and duodenal stenosis was present. Parental studies show maternal glucose intolerance but normal pancreatic exocrine function and upper G.I. series. These infants demonstrate that absence of fetal insulin and glucagon yields severe IUGR and failure of neonatal fuel homeostasis.

LABORATORY STUDIES IN PATIENTS WITH REYES SYNDROME. A.L. Smith, F. H. Lovejoy and M. Bresnan. (Intr. by David H. Smith) Children's Hospital Medical Center, Dept. of Med., Boston, Mass.

Fifteen patients with Reyes Syndrome were prospectively studied according to a protocol designed to describe the course of the illness biochemically. Therapy consisted of careful fluid, electrolyte, acid-base and respiratory management. All patients demonstrated an increase in blood FFA ($m = 3.1 \text{ meq/L}$), blood lactate ($m = 2.8 \text{ mM}$), blood β -hydroxybutyrate ($m = 1.5\text{mM}$) and a decrease in plasma triglycerides ($m = 38 \text{ mg}\%$). The magnitude of these changes in stages II or III did not differentiate between ultimate survivors and non-survivors. Hypoglycemia occurred in two patients and was easily corrected by the administration of 5% glucose. This metabolic pattern is compatible with the hypothesis that Reyes Syndrome is characterized by a deficiency of glucose oxidation. If this hypothesis is correct, then the other observed abnormal laboratory findings (eg. an increase in serum CPK, amylase, and OCT activities an elevation in blood NH_3 concentration; abnormal EEG, ST and T wave changes on EKG) which are accepted features of the illness may reflect multiple organ system involvement by the same process. A decrease in blood β -hydroxybutyrate concentration, suggesting a failure of ketogenesis, occurred in 5/5 clinical stage IV patients who ultimately expired.

Decreased glucose oxidation appears to play role in the pathogenesis of Reyes Syndrome.