METHYLMALONYLCoA CARBONYLMUTASE (MUTASE) ACTIVITY IN VIVO AND IN VITRO-FURTHER EVIDENCE OF GENETIC HETEROGENEITY, Grant Morrow III, M.J.Mahoney, J.Lebowitz, T.R.Whitaker and A.J. Giorgio. Univ. of Arizona, Dept. of Ped.; Yale Univ., Dept. of Human Genetics; and Univ. of Pittsburgh, Dept. of Med.

Patients with the genetic defect, methylmalonic acidemia (MM-emia), have vomiting, ketoacidosis, failure to thrive and a high mortality. Clinically, patients are usually classified by their in vivo response to vitamin B_{12} i.e. some tend to normalize biochemically whereas others do not. Cell free extracts of liver and/or skin fibroblasts were assayed for mutase activity by measuring succinate formation from methylmalonylCoA. Vitamin B_{12} coenzyme (DBCC) synthesis was measured by incorporation of Co^{57} precursor into DBCC. 5 patients, clinically unresponsive, had no in vitro mutase activity and synthesized DBCC normally. 4 additional patients had normal in vitro mutase activity and defective DBCC formation. However, only 2 of the 4 were responsive in vivo. Intact fibroblasts were studied for conversion of propionate-1-^{14}C to $^{14}CO_2$. Good correlation of $^{14}CO_2$ production was noted in the 5 lines with no mutase activity but variable results were found in the other 4.

Liver mutase activity accurately reflects fibroblast extract activity in any individual patient. Response by intact cells to B_{12} is variable in some patients. "Responsiveness" should be limited to the changes noted in vivo and should remain a clinical description rather than one to delineate possible mechanisms responsible for the defect.

EFFECT OF PARATHYROID EXTRACT ON BICARBONATE INDUCED HYPOCALCEMIA IN THE RAT. Cecilia T. Nervez, Roger J. Shott, Margaret L. Williams and William H. Bergstrom. Dept. of Pediatrics, Upstate Medical Center, Syracuse, N.Y.

Hypocalcemia often follows $NaHCO_3$ therapy for acidosis in premature infants. The correlation of this phenomenon with weight and gestational age suggests that functional hypoparathyroidism may permit a substantial shift of calcium to bone when H^+ concentration falls.

We find that rats injected with $NaHCO_3$ show hypocalcemia inversely proportional to age. Post injection levels were 9.3 mg% in 350 gm rats, 8.3 mg% at 65 gm, and 7.6 mg% at 7 gm. Subcutaneous injection of parathyroid extract (PTE) prevented the hypocalcemic response to bicarbonate. This protective effect was present at 2, 4 and 8 hours after PTE injection but was gone by 16 hours. At the same intervals, rats receiving PTE but no $NaHCO_3$ were not hypercalcemic.

The ability of PTE to avert post-bicarbonate hypocalcemia is consistent with the view that bone is the site of calcium sequestration. The duration of PTE effect and the absence of hypercalcemia suggest the possibility that PTE may be clinically useful if the response of the human neonate proves to be analogous to that of the infant rat.

PITFALLS IN DIFFERENTIAL HEAT INACTIVATION OF HEXOS-AMINIDASE FOR HETEROZYGOTE DETECTION FOR TAY-SACHS DISEASE (TSD). H. M. Nitowsky, S. Nakagawa and S. Kumin. Depts. Ped. and Gen., Albert Einstein Coll. Med., Bronx, N.Y.

Serum hexosaminidase A (hex A) activity is reduced in obligate carriers of the TSD gene. The heat lability of hex A when exposed to 50-52°C under standard conditions has been employed for carrier detection in mass screening programs. Our experience with a program involving tests on more than 3,500 persons has revealed more than 50% false positives on retesting by independent and more sensitive methods. Moreover, thermal lability tests of serum from obligate heterozygotes have shown at least a 15% overlap with normals. Assay of leukocyte hex A also lacks sufficient precision because hex B in white cell extracts is significantly less heat stable than in serum. Application of DEAE ion exchange chromatography for separation and quantitation of hex A yields better discrimination of heterozygotes from noncarriers (noncarrier 10.0 ± 1.22; obligate heterozygotes 4.6 ± 1.20; newly identified carriers 5.1 ± 0.95 in nM/ml/min). A large "I" component can be separated from serum and tissues from TSD patients, and intermediate levels are observed in carriers. The "I" fraction is indistinguishable from hex B by kinetic or thermal stability properties, and resembles the "P" fraction observed during pregnancy. Our studies suggest that hex A deficiency in TSD may reflect an abnormality in "enzyme realization" - i.e. conversion of hex A from a precursor protein.

ENVIRONMENTAL CONTRIBUTION TO BLOOD LEAD LEVELS IN INFANCY Richard G. Osborne, John R. Raye, Martha L. Lepow UConn Med. Sch., Dept. Ped., Farmington, Ct.

Data have not previously been presented which allow for separation of the relative role of pica from general environmental lead contamination in the development of high blood lead levels in childhood. This study has examined the lead levels in cord and maternal blood and related these values to sources of maternal environmental lead exposure. Infants were then followed prospectively to assess subsequent lead accumulation. Mean maternal blood lead level (n=114) was $1.29 \pm .51$ μ moles/LRBC and values were significantly influenced ($p < .05$) by race (Puerto Rican > Black > White), urban location, and age of dwelling, but not by social class or smoking. Mean newborn blood lead level (n=182) was $1.00 \pm .51$ μ moles/LRBC and values were similarily influenced by maternal race, location and age of dwelling as well as by direct proximity of dwelling to high traffic flow. There was linear relationship between paired maternal and newborn lead levels ($r=.687$., $p < .001$). After birth the rise in subsequent blood lead determinations was gradual over the first 18 months of life without evidence of a sudden rise at the age of ambulation. These data suggest that certain environmental factors play a major role in defining a group of infants who are "at risk" for developing high blood lead levels even prior to the development of pica. Exposure to this environment starts in utero.

HYPERGLYCEMIA IN LOW BIRTH WEIGHT INFANTS (LBWI). R.S. Pildes, M. Zarif and D. Vidyasagar. Cook County Hospital and Univ. of Ill. Coll. of Med., Depts of Pediatrics, Chicago, Ill.

The metabolic responses of 75 LBWI subjected to "routine nursery regimes" were studied prospectively for the 1st 5 days of life. Glucose (10%) was given via infusion pumps at a mean (±S.E.) rate of 4.4±.2mg/kg/min (range 3-7) for the 1st 2 days and was weaned slowly. Oral feedings were started as tolerated. The mean birth wt. was 1394±47g (range, 567-2000g); there were 60AGA, 11SGA and 4LGA infants. Blood glucose values were significantly higher on days 1 and 2 (125±19 and 94±13mg% respectively) than on days 3 and 5 (65±5 and 66±5mg%) reflecting the decreased use of I.V. fluids after day 2. Hypoglycemia (blood glucose <20mg%) occured in 2 SGA and 1 AGA before I.V. fluids were started (<3 hrs. of age). On the other hand, hyperglycemia (>150mg%, range 152-875mg%) was found in 27 of 75 infants. Moreover, hyperglycemia was seen in a significantly ($p<0.001$) greater proportion of IBWI who died (18/24) than in those who lived (9/51). Plasma insulin values were significantly higher on days 1 and 2 (15±3 and 18±4uU/ml) than on days 3 and 4-5 (6±1 and 7±2uU/ml) indicating the ability of the LBWI's pancreas to respond to hypertonic glucose. Plasma growth hormone values were significantly lower after the 3rd day when glucose values were low than during the 1st 3 days when glucose values were high. Although a direct causal relationship between I.V. glucose, hyperglycemia and mortality cannot be made, careful monitoring of blood glucose in LBWI is indicated even if the amounts of glucose infused are relatively small.

THE BIOCHEMICAL EXPLANATION FOR LACK OF PHOTOSENSITIVITY IN Pb INTOXICATION. S. Piomelli, A. Lomola, E. Carlos, C. Seaman, M. Poh-Fitzpatrick, L. Harber, Dept. Ped., NYU; Dept. Dermatol., Columbia Univ., N.Y. and Bell Lab., Murray Hill, NJ

This study explored the lack of photosensitivity in childhood Pb intoxication (CPI), despite RBCs protoporphyrin (PP) levels often higher than in erythropoietic protoporphyria (EPP).

PP was bound to Hgb in both CPI and EPP. Absorption and emission of EPP Hgb solutions were identical to those of protein bound PP (405 and 620 nm); CPI Hgb solutions instead peaked at 424 and 590 nm. Acetone easily detached PP from Hgb in EPP, but not in CPI. The persistence of PP "in vivo" was measured in RBCs separated according to age on discontinuous gradients of arabino-galactan. In CPI, PP decreased only slightly during the RBCs life span and all cells faintly fluoresced. In EPP, PP decreased rapidly "in vivo", at a rate parallel to reticulocytes; all young RBCs had intense fluorescence, which disappeared at similar rate. Plasma PP levels were normal in CPI, but elevated in EPP.

These data indicate that in CPI the relative excess of PP occupies some of the heme sites, available because of defective heme synthesis. In EPP, heme synthesis is normal, and excess PP binds to the surface of the Hgb molecule. Thus, in CPI, the PP remains within the RBC through its life span and cannot (as in EPP) diffuse through the plasma into the skin to induce photosensitivity.