ALTERATIONS OF THE OXYGEN HEMOGLOBIN EQUILIBRIUM CURVE AND RED CELL 2,3-DIPHOSPHOGLYCERATE(2,3-DPG) IN CORD BLOOD OF INFANTS BORN TO OPIATE-DEPENDENT WOMEN. L.P.Finnegan, Z.Shouraie, J.P. Emich, J.F.Connaughton, J.Schut and M.Delivoria-Papadopoulos, Phila. Gen. Hosp. Univ. of Penna. Sch. of Med. Phila., Pa.

The absence of hyaline membrane disease (HMD) in low birthweight infants of heroin addicted mothers may be due to accelerated lung maturation in utero as shown in fetal rabbits. The aim of the present studies was to assess the tissue oxygenation of infants born to opiate-dependent mothers and relate it to the clinically documented absence of HMD. The cord bloods of 14 infants weighing between 1650 and 3460 grams at birth were obtained as well as maternal venous blood. Measurements of the $P_{50}$ (partial pressure of oxygen at which hemoglobin is 50% saturated) hematocrit and red cell DPG were performed in maternal and fetal bloods. All infants monitored for signs and symptoms of HMD showed no evidence of disease. Mean values of $P_{50}$ in the cord blood were 24.0 mmHg as compared to 19.5 mmHg in control infants, total 2,3-DPG was 7458 muM/ml of RBC as compared to 5433 in normal controls. Maternal values were slightly elevated for both ($P_{50}$,2,3-DPG) as compared to normal controls. This shift of the curve to the right is achieved in term infants by the 6th-9th week of life under normal conditions. It seems that newborns of opiate-dependent mothers achieve tissue oxygen unloading comparable to that of a 6 week old term infant suggesting that opiates may function as enzyme inducers resulting in increased blood levels of 2,3-DPG and a decrease in $O_2$ affinity.

COARSE FACIES, ACROMEGALOID FEATURES AND LOW SERUM THYROXINE IN A BOY ON LONG-TERM ANTICONVULSANT THERAPY. Lytt I.Gardner Lee Ann Wallach and Tania Gregory. State Univ. of New York, Upstate Med. Ctr.,Dept. of Peds., Syracuse, NY

Chronic diphenylhydantoin therapy has long been known to be associated with gum hypertrophy; there are scattered descriptions of more generalized tissue proliferation. The present observations were made on a 17 year old boy, one of fraternal twins, who has been on various combinations of diphenylhydantoin, mephobarbital and primidone for the last 5 years because of a seizure disorder. His facies were coarse and acromegaloid, with the suggestion of edema. Hands and feet were normal in size. Height was 68 in. with a linear growth curve since infancy identical with that of his normal twin. Bone age was normal. Serum growth hormone assays done during a glucose tolerance test revealed no abnormal increase of growth hormone. Serum values both of thyroxine by competitive protein binding and of free thyroxine were low ($T_4$CPB = 2.7 µg.% as iodine; $FT_4$ = 0.7 µg.% as iodine). It is tempting to hypothesize that the anticonvulsants have produced an iatrogenic metabolic error of thyroxine metabolism in which the "myxedema" effect predominates. Obviously there has been no hypothyroidism-like effect on linear growth or osseous maturation. It is known that diphenylhydantoin is bound to TBG and may block thyroxine. In addition diphenylhydantoin and certain barbitals may cause adaptation of hydrolase enzymes so as to increase degradation of thyroxine and precursors.

**Salivary Electrolytes in Infants Receiving Digoxin.** **Constance J. Hayes, Stephen Wotman, Allan Hordof, Stuart Epstein and Walton M. Gersony. Division of Preventive Dentistry, School of Dental and Oral Surgery, Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, New York.**

**Recent adult studies have suggested an increase in salivary K+ and Ca++ in patients receiving digitalis. In order to investigate this phenomenon in the pediatric patient, whole saliva electrolytes were studied in 32 hospitalized infants (mean age 10 weeks); 17 receiving digoxin (mean digoxin level 2.1ng/ml) and 15 controls. Simultaneous serum electrolytes were also measured. Mean salivary K+ was significantly increased, 25.4±3.7mEq/l in the digitalized infants when compared to controls, 21.6±3.3mEq/l ($p < .01$). Mean salivary Ca++ was also elevated in the infants receiving digoxin, 4.3±2.8mEq/l versus controls 3.0±.94mEq/l ($p < .05$). The K+ x Ca++ product was 111.4±84.0 in infants receiving digoxin and 65.3±27.1 for controls ($p < .025$). Salivary Na+ was not different in the two groups. Serum K+ was elevated in the group receiving digoxin 5.1±69 as compared to controls 4.6±.68 ($p < .05$) but serum Ca++ and Na+ concentration were similar. The mean salivary electrolyte concentrations in control infants and those receiving digoxin were comparable to levels reported for adults. The increase in K+ concentration in saliva of infants receiving digoxin with no change in salivary Na+ lends support to the hypothesis that the increase in K+ in saliva is due to K+ loss from cells or elevated plasma K+ rather than inhibition of Na+/K+ exchange.**

MATERNAL DRUG INGESTION AND LACTATION. Reba M. Hill, Marjorie G. Horning, Lee B. McCulley and Jean Nowlin, (Intr. by Louis L. Hill). Dept. of Ped., Inst. for Lipid Research, Baylor Col. of Med., St. Luke's Episcopal Hosp., Houston, Texas.

Quantification and identification of drugs in human colostrum and breast milk have been accomplished by selective ion detection using a gas chromatograph-mass spectrometer-computer system. Drugs routinely administered to gravid females for acute as well as chronic indication in the pre and postpartum period were studied.

Sixteen hours after the last maternal dose (30 mg q.i.d.) of phenobarbital the breast milk level was found to be 2.74 µg/ml. Oral ingestion of a short or intermediate acting barbiturate such as pentobarbital or butabarbital resulted in lower concentrations, i.e., .17 µg/ml 19 hours after ingestion and .37 µg/ml 1.5 hours after ingestion respectively. Intravenous administration of 15 mg of diazepam during labor resulted in a colostrum level of .10 µg/ml 25½ hours later. The level of diphenylhydantoin in breast milk 3 hours after a single 100 mg oral dose was 4.2 µg/ml with a decline to 1 µg/ml at 6 hours. Levels of .5 - 1.5 µg/ml were then obtained for the ensuing 18 hours. Additional drugs identified in breast milk but not quantified were secobarbital, ethosuximide, codeine, methadone, tolbutamide and caffeine.

No obvious effects of the drugs were observed in these neonates, but breast milk may serve as a significant route for neonatal drug ingestion particularly when drugs are consumed daily or the drug consumed has prolonged activity.

NEONATAL WITHDRAWAL FROM TRANSPLACENTALLY ACQUIRED MEPHOBARBITAL. Reba M. Hill, Marjorie G. Horning, Naoma F. Morgan, and Jean Nowlin, (Intr. by L. Leighton Hill). Dept. of Ped., Inst. for Lipid Research, Baylor Col. of Med., St. Luke's Episcopal Hospital, Houston, Texas 77025.

Withdrawal symptoms consisting of severe tremors, irritability, opisthotonos and increased muscle tonus were observed in two siblings born to a mother requiring mephobarbital for control of seizures. Both infants manifested symptoms within the first minutes of life and continued to be symptomatic for 2-6 months after delivery. At birth the infants were small for gestation and had some of the physical findings (Hill, et al) observed in infants exposed to intrauterine anticonvulsant drugs. Somatic growth during the first 4 years and 18 months of life, respectively, was normal but mental development in the second infant at 18 months of age was slow (D.Q. 83).

Placental transfer of mephobarbital was documented in both infants by selective ion detection using a gas chromatograph-mass spectrometer-computer system. Prolonged excretion of mephobarbital and phenobarbital was demonstrated in the second infant. At the time of delivery the maternal urine contained 17.22 µg/ml of phenobarbital and 1.15 µg/ml of mephobarbital. Urine collected from the infant between 10-27 hours of age contained 13.15 µg/ml of phenobarbital and .88 µg/ml of mephobarbital. Subsequent samples examined on 5, 8, 10, 15 and 22 days of age revealed continued excretion of phenobarbital (.13 µg/ml) through the last sampling period.

USE OF RADIOIMMUNOASSAY TO STUDY DIPHENYLHYDANTOIN PHARMACOKINETICS IN CHILDREN. Michael V. Johnston, Robert H.A. Haslam, and Paul S. Lietman, The Johns Hopkins University, The Johns Hopkins Hospital, Department of Pediatrics, Baltimore, Maryland.

The detailed study of the kinetics of the anticonvulsant, diphenylhydantoin (DPH), in small children has been difficult with conventional gas chromatographic (GLC) methods. A new radioimmunoassay (RIA) developed by Cook and Christensen (Res. Comm. Chem. Path. Pharmacol. 5: 767, 1973) was duplicated in our laboratory and some of the characteristics of the assay defined. The sensitivity of this assay allowed DPH levels to be determined accurately in 20 µl of plasma. The antibody is highly specific for DPH and the assay correlates well with GLC. In several infants being treated for seizures with a commonly used dose, plasma DPH levels were found to be low. The RIA method facilitated monitoring their plasma levels. When plasma levels were measured following an IV dose of DPH, the infants were found to metabolize the drug more rapidly than did adolescents and adults.