247 DIETARY INFLUENCES ON THEOPHYLLINE PHARMACOKINETICS IN CHILDREN. Charles H. Feldman, Vincent E. Hutchinson, Charles Pippenger, Bernard R. Feldman, and William J. Davis, (Spon. by Jerry C. Jacobs) College of Physicians and Surgeons, Columbia University, Dept. of Pediatrics, New York.

We have examined the influence of diet on theophylline (T) pharmacokinetics in 14 asthmatic children, receiving chronic oral T. Doses from 4.2-8.8 mg/kg were given in an amount determined to yield therapeutic serum levels. Each patient was placed on 3 separate diets with different proportions of protein and carbohydrate and with constant fat and calories. Sequential serum T levels were obtained following a single oral dose on day 12 of each test diet. T half-life ($t_{1/2}$) decreased on high protein (P) diet to a mean of 4.75 hr. compared to 6.76 on normal (N) diet and increased to 18.10 on high carbohydrate (C) diet (both $p < .001$). The metabolic clearance rate rose from a mean of .045 L/kg/hr on N to .055 on P and decreased to .037 during C (both $p < .001$). The apparent volume of distribution remained unchanged, except for an increase from .423 L/kg to .988 on C ($p < .01$). Multiple linear regression function demonstrated $t_{1/2}$ differences to correlate significantly only with dietary changes. No abnormal blood chemistries were detected during any test periods. These results clearly show the effect of diet on T pharmacokinetics in children.

248 THE INCIDENCE OF SUDDEN DEATH IN INFANTS BORN TO WOMEN MAINTAINED ON METHADONE. Loretta P. Finnegan, Dian S. Reeser, (Spon. by Leonard J. Graziani), Jefferson Medical College, Dept. of Pediatrics, Philadelphia, PA

It has been suggested that sudden infant death syndrome (SIDS) is increased in infants born to methadone maintained women (MMW). In a series of 354 infants of MMW during pregnancy, 5 cases of SIDS have been identified. All mothers had prenatal care and 3, all multiparous, had major obstetrical complications. Daily methadone was between 10 and 50 mg. for 2 wks. to 8 mos. The infants were of 40 wks. gestation; Apgar scores were ≥ 8 at 1 and 5 min. in 4 infants, one had scores ≤ 6; birth weights were between 2570 and 3085 gms.; one was treated for methadone withdrawal. During their nursery stay, 2 developed physiologic jaundice; 2 had hypocalcemia; 1 had mild gastroenteritis with negative culture results; 1 had meconium aspiration pneumonia. All infants died at home between 31 days and 5 mos.; complete postmortem examinations, including toxicologies in 4, were performed. Cause of death in all cases was SIDS, with pulmonary congestion being the most frequent pathological diagnosis. Our series supports previous suggestions that the incidence of SIDS is markedly increased from the overall expected incidence of 0.25% to 1.4%. Since an association of chronic hypoxemia and SIDS has been suggested, a possible hypothesis for the increased incidence in infants who have suffered the effects of prenatal drug abuse may be that repeated insults during maternal overdose and/or withdrawal produce a milieu predisposing the fetus to chronic fetal hypoxemia which increases the chances for SIDS. (Supported by NIDA Grant #DA01807 and Commonwealth of Pa. Contract #1674.)

249 CHLORAMPHENICOL KINETICS IN INFANTS AND CHILDREN C.A. Friedman, F.C. Lovejoy, and A.L. Smith, Children's Hospital Medical Center, Divisions of Infectious Disease and Pharmacology, Boston, Massachusetts

We studied the disposition of chloramphenicol after intravenous administration to 56 infants and children aged one day to 11 years at doses ranging from 12.5 to 100 mg/Kg/day. The mean T 1/2 was 5.94 hrs (range 0.87 - 17.8 hrs); neonates had a longer T 1/2, 8.01 hrs, but not statistically different from non neonates, 5.54 hrs ($p = 0.12$). The T 1/2 of patients who weighed < 10 kg was longer than that of those weighing > 10 kg (9.02 vs 4.55 hrs; $p < 0.001$). In 17 patients the pharmacologic peak concentration (C_0) standardized for dose linearly correlated with dosage based on body surface area ($r = 0.61$) or body weight ($r = 0.60$). The C_0 values, however, were highly variable; serum concentrations ranged from 0.39 to 2.43 µg/ml per mg per kg administered ($\bar{m} = 0.97$ µg/ml). Eight patients had T 1/2 values which approached infinity; in all eight the concentration of total serum chloramphenicol compounds was greater than biologically active drug during the 8 hour observation period. Four of these 8 patients were hypotensive at the time of the study, but none had laboratory evidence of renal or hepatic failure. One-half of these 8 patients on re-study after clinical improvement had T 1/2 between 4.02 and 20.8 hrs. We conclude that there is a marked individual variation in chloramphenicol pharmacokinetics which is, in part, explicable by delayed hydrolysis of the succinate ester and decreased excretion.

250 INDOMETHACIN DISPOSITION IN PREMATURE INFANTS: BLEEDING DUE TO PLATELET DYSFUNCTION AFTER SINGLE DOSES OF INDOMETHACIN. Zvi Friedman, Victor Whitman, M. Jeffrey Maisels, William Berman, Keith H. Marks, Elliot S. Vesell. Penn State Univ Coll Med, M. S. Hershey Med Ctr, Dept Ped and Pharm, Hershey, PA.

Indomethacin failed to produce permanent ductal closure in any of four premature infants with patent ductus arteriosus to whom the drug was given (0.15-0.30 mg/kg). Indomethacin half-lives measured in two premature infants were 21 and 24 hours, much longer than in full-term newborns or adults. Platelet function, as measured by platelet aggregation, was grossly abnormal for two to four days after indomethacin administration, normal values returning only by the ninth and tenth day. Gastrointestinal bleeding and transient renal dysfunction occurred in one infant. Measurement of plasma indomethacin concentrations in sick, low birthweight infants could help to monitor indomethacin dose and dosage interval, thereby preventing drug accumulation and reducing toxicity. Further studies of potential toxicity seem to be indicated before instituting widespread indomethacin administration for ductal closure in premature infants.

251 ADVERSE EFFECT OF MATERNAL MEDICATION ON TEMPERATURE OF NEONATES. Saraswathy K. Ganapathy, Yvonne D'Sylva, Lois L. Neumann and Angelo Ferrara (Spon. by Robert G. Schacht). Dept of Peds., NYU School of Medicine, New York, N.Y.

The effect of meperidine, promazine and scopolamine given to women in labor on the temperature of the newborn (NB) on admission to the nursery was studied. 475 healthy term vaginally delivered NB (BW 2500-4000 gm, 1 min Apgar > 6) were reviewed. Delivery rooms were maintained at 23-24°C and there was no significant difference between cold (< 36°C) and warm babies in time of arrival in nursery. 113 women received medications for pain relief. Some women in both medicated and non-medicated groups received regional anesthesia (RA). The incidence of hypothermia in the infants is shown below:

Med/RA	N	% Cold	
Med $\bar{c}$ RA	94	21.2	χ^2 4.07
No Med $\bar{c}$ RA	347	12.4	P >.05(significant)
Med $\bar{c}$ & $\bar{s}$ RA	113	20.3	χ^2 3.4
No Med $\bar{c}$ & $\bar{s}$ RA	362	12.7	.05>P>.1(borderline)

A significant increase in percentage of cold NB was noted in the medicated group whose mothers received regional anesthesia. The difference was less apparent when mothers without regional anesthesia were also included (numbers small). Meperidine causes peripheral vasodilatation which may cause the hypothermia noted.

252 DISPOSITION OF CHLORAMPHENICOL IN NEWBORN INFANTS. John P. Glazer, Michele Danish, Stephen Yachetti, and W. Stuart Warren (Spon. by Sumner J. Yaffe) University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia, Dept. of Pediatrics, Philadelphia.

Time-concentration curves were determined following intravenous administration of chloramphenicol sodium succinate (CL) to 11 infants with suspected septicemia, using a gas-liquid chromatographic assay. 2 groups of infants were studied. Group I, consisting of 6 infants 2-8 days of age and between 0.9 and 2.5 kg, received 25 mg/kg once daily. Group II, consisting of 5 infants 11 days to 8 weeks of age and between 0.9 and 2.2 kg, received 50 mg/kg/day in 2-3 divided doses. Three key observations were made. First, 5 group I infants cleared CL so slowly that half-lives could not be calculated on the basis of serial serum levels determined in the interval between doses, whereas group II infants cleared CL much more rapidly, with half-lives ranging from 5.2 to 12.8 hours. These observed differences in CL disposition are consistent with maturational differences in hepatic uptake and/or glucuronidation. Second, within group II, there was no consistent corelation between half-life and gestational age. Third, in both groups, there were some patients whose peak CL levels were markedly lower than anticipated. Since only hydrolyzed CL is detected by our assay, this observation is consistent with the concept that CL esterase activity may vary among neonates. Significant interpatient variability in CL disposition within postnatal/gestational age categories mandates monitoring of CL levels in neonates treated with this drug.