●380 ALTERATIONS IN THEOPHYLLINE (T) METABOLISM DURING THE FIRST YEAR OF LIFE. Donna M. Kraus, James H. Fischer, Susan A. Kecskes, Shirley J. Reitz, Tsu F. Yeh, Kristine McCulloch, Michael J. Cwik. University of Illinois at Chicago, University of Illinois and Cook County Hospitals, Departments of Pharmacy Practice and Pediatrics, Chicago.

Maturational changes in T pharmacokinetics were evaluated in 45 infants; postconceptional age (PCA) 30.9-95.7 wks. After achievement of steady-state on T maintenance therapy, multiple serum and urine samples were obtained over dosing interval and assayed by HPLC for T and metabolites: caffeine (C), 1-methyl uric acid (1MU), 3-methylxanthine (3MX), 1,3-dimethyluric acid (1,3MU). Mean(SD) T clearance (Cl) increased significantly ($p<0.05$; ANOVA) for PCA groups at 30-40, 40-50 and >50 wks from 21.9(6.3) to 26.6(7.7) and 57.7(17.6) ml/hr/kg, respectively. Concomitant decrease ($p<0.05$) in serum C/T ratio was observed for same PCA groups; 0.43(0.15), 0.22(0.07) and 0.06(0.1), respectively. Significant serum C concentrations (C/T>0.10) were found in some infants up to 55 weeks PCA. Stepwise multiple regression analysis showed urinary excretion of 3MX to be the primary parameter explaining the change in both T Cl ($r=0.81$, $p<0.01$) and serum C/T ratio ($r=0.66$, $p<0.01$). Urinary excretion of 3MX (demethylated) for the 3 PCA groups was 1.4, 4.2 and 13.1% compared to 23%, 41% and 44% for 1,3MU (oxidative). Disappearance of serum C and maturation of T metabolism is dependent on development of demethylation pathway which does not occur until approximately 55 wks PCA. Prior to that age, serum C concentration should be monitored in patients receiving T.

381 **DESORPTION OF ASPIRIN FROM ACTIVATED CHARCOAL.** **Peter G. Lacouture, Susan Fish, Gay Filippone, Joseph Scavone, Frederick H. Lovejoy. Harvard Medical School, Children's Hospital, Dept. of Medicine, Boston, MA.**

We studied the potential desorption of aspirin (ASA) from activated charcoal (AC) in 8 volunteers in a cross-over study. Separated by 10 days, subjects received either 1 gm of ASA in solution or a slurry of 1 gm of ASA with 10 gm of AC. Complete binding of ASA to AC was assured by assay of the effluent. These solutions were incubated for 15 minutes before ingestion. Blood was obtained at 0, .5, 1, 2, 4, 6, 8, 10, 12, 24 and 30 hrs post ingestion and plasma salicylate concentrations were determined by HPLC.

GROUP	Cmax (mcg/ml)	Tmax (hrs)	AUC (mcg/ml hr)
ASA	59.4*	1.6	475.6*
ASA/AC	9.4	2.8*	88.5

*** significantly greater $p<0.05$**

Our results further demonstrate that (1) the t1/2 between 4 and 12 hrs was not different in the ASA (5.5 hrs) and ASA/AC (4.6 hrs) groups ($p>0.05$); (2) the t1/2 was different in the ASA (5.5 hrs) and ASA/AC (21.8 hrs) groups between 12 and 30 hrs and (3) ASA concentrations were greater at 24 and 30 hrs in the ASA/AC vs ASA group ($p<0.05$). We conclude that in these doses, ASA binding to AC is reversible and may act as a delayed release preparation.

●382 THE EFFECT OF DIETHYLHEXYL ADIPATE (DEHA) ON CYTOCHROME P-450 (P-450) IN NONPREGNANT (NP) AND PREGNANT (P) MICE. George H. Lambert, Helen Lietz, Nancy Hassinger, John Micheals. (Spon. A.Cutilletta) Loyola U., Stritch School of Med., Dept. of Peds., Maywood, IL., and U. of Chicago, Chicago, IL.

DEHA, a chemical used in plastic food wrap and cosmetics, causes intrauterine growth retardation and fetal abnormalities in rats, decreases fertility in mice and is a hepatocarcinogen. Since changes in P-450 activity can alter both carcinogenic and teratogenic activity, we studied the effect of DEHA on hepatic P-450 in P and NP C57BL/6J mice using aminopyrine-N-demethylase activity (APD), P-450 content and HPLC isozyme pattern in non-treated (NT) and treated (T) females. Mice were treated with 1 intraperitoneal injection of DEHA (12.5 ml/kg body weight) 48 hrs before preparation of hepatic microsomes.

In NP mice, DEHA increased P-450 content (NT = 0.80 ± 0.11, T = 1.11 ± 0.05 nmoles/mg protein $p< 0.001$) but did not alter APD activity, (NT = 14.7 ± 1.9, T = 16.3 ± 5.3 nmoles HCHO/min/mg protein). In P mice treated on day 15 of gestation, DEHA increased both P-450 (NT = 0.67 ± 0.06, T = 0.92 ± 0.12 nmoles/mg protein, $p< 0.001$) and APD (NT = 7.0 ± 0.1, T = 14.0 ± 2.8 nmoles HCHO/min/mg protein $p< 0.001$). HPLC elution patterns confirmed DEHA induction of P-450 constitutive isozymes and demonstrated that P-450-gest, an isozyme induced in mouse pregnancy (Biochem Pharm, in press), was decreased by DEHA treatment.

In conclusion, DEHA increased P-450 content in NP and P mice but increased APD only in P mice. In the P mouse, DEHA decreased P-450-gest but increased other P-450 isozymes. Future studies are needed to determine if the reproductive effects of DEHA are mediated through changes in P-450 isozymes.

●383 EFFECT OF INDOMETHACIN (Id) ON THE CEREBRAL BLOOD FLOW VELOCITY (CBFV) OF PREMATURE NEWBORNS (prem NB). N. Laudignon, S. Chemtob, H. Bard, J.V. Aranda Depts. of Peds. and Pharmacology, McGill Univ. Montreal Children's and Ste Justine Hosp, Montreal, Canada.

Low doses of Id may decrease the incidence of intraventricular hemorrhage in prem NB, but its effect on immature cerebral vasculature and more specifically post endotracheal suctioning is unknown. Using Doppler technique, 13 prem NB treated with Id for the treatment of patent ductus arteriosus were studied. CBFV of anterior cerebral arteries calculated from the area under the velocity curve (AUTC/min), heart rate (HR), and mean arterial pressure (MABP) were recorded before and 15, 30, 45, 60, and 120 min after the 1st IV injection of Id 0.2 mg/kg (group 1, BW: 1269 ± 353 gm, GA: 29 ± 2 wks), and the 3rd injection (group 2, BW: 1490 ± 459 gm, GA: 30 ± 3 wks). Capillary blood gases were obtained before and 60 min after drug injection. MABP, HR, blood gases and pulsatility index were stable throughout the study in both groups. The 1st dose of Id decreased CBFV at 15 min by 22%, and was sustained till 120 min (-28%, $p<0.005$). CBFV values before 1st and 3rd injection were comparable. CBFV did not change after the 3rd dose. In 5 mechanically ventilated infants, AUTC was also measured pre and post endotracheal suctioning, before and 60 min after each injection. In group 1, the percent increase in CBFV secondary to suctioning was 21.38 ± 27.26 % before Id and 2.77 ± 28.45% 60 min after Id ($p<0.02$). In contrast, CBFV changes were not significantly affected by the 3rd dose. Thus, an initial dose of Id: 1) decreases resting CBFV, and 2) may attenuate CBFV fluctuations in the prem NB.

384 EFFECTS OF INTRAUTERINE EXPOSURE TO ALKALOIDAL COCAINE ("CRACK"). Patrick LeBlanc, Aruna Parekh, Barbara Naso, Leonard Glass. Department of Pediatrics, SUNY/H.S.C., Brooklyn, N.Y.

Thirty eight infants born to mothers using crack were studied over a 4 month period. None of the mothers were known to have used IV cocaine or opiates during pregnancy.

Birth weights ranged from 1.30 to 3.98 kg, (median 2.69 kg); g.a. ranged from 31 to 40 weeks, (median 38 weeks). Ten (26%) had a b.w. of less than 2.5 kg. and/or a g.a. of 37 weeks or less.

Eighteen (47%) demonstrated abnormal neuromuscular signs. Sixteen had tremors, with onset on day 1-5 (median day 2). Duration ranged from 1 to 20 days, (median of 3 days), and were present in only one infant for more than 1 week. Sixteen infants demonstrated irritability with onset on day 1-4 (median day 2). Duration ranged from 1 to 22 days, (median of 3 days), and persisted for more than 1 week in 2 infants (9 and 22 days). Eleven infants showed signs of muscular rigidity, with onset on day 1-5, (median day 2). In 9, rigidity had disappeared by the end of the first week, and in 2 persisted into early infancy. Five infants required phenobarbital therapy.

Our data suggest that while transient neurologic symptoms in these infants are common, persistent overt findings are unusual.

●385 DRUG METABOLITE TOXICITY ASSESSED IN HUMAN LYMPHOCYTES WITH A PURIFIED, RECONSTITUTED CYTOCHROME P-450 SYSTEM J. Steven Leeder, Marilyn Cannon, Azima Nakhooda, Stephen P. Spielberg. University of Toronto,The Hospital for Sick Children, Research Institute, Division of Clinical Pharmacology, Toronto, Ontario.

We have developed a new cytotoxicity assay to study cellular detoxification capacity. Human lymphocytes are exposed in vitro to reactive acetaminophen (APAP) metabolites generated by purified and reconstituted rat cytochrome P-450 and NADPH-dependent cytochrome P-450 reductase. Cells (2×10^5) are incubated with APAP, 12 pmol P-450, 0.015 units of reductase, and an NADPH generating system in a microtitre plate well (250 µl total volume) for 2 hours at 37°C, washed, resuspended in 5 µg/ml albumin in HEPES and incubated for a further 16 hours at 37°C before assessment of cell death. Viability is based on the ability of live cells to reduce the tetrazolium salt MTT to a purple formazan which is measured with a multiwell scanning spectrophototometer. APAP toxicity, expressed as the percentage dead cells, is dependent on the presence of P-450 and NADPH, and can be inhibited by 25 µM SKF 525A. To validate this assay, lymphocytes from a patient with glutathione synthetase (GSH-S) deficiency and 10 control subjects were challenged in vitro. Those of the GSH-S deficient patient exhibited toxicity to APAP which exceeded the 95% confidence limits of the control subjects over a concentration range of 10 - 1000 µg/ml : 7.0% toxicity at 10 µg/ml (control 95% confidence limit 0 - 0.4 %), 24.6% toxicity (3.9 - 9.5%) at 100 µg/ml and 43.1% toxicity (23.0 - 32.1%) at 1000 µg/ml. The data indicate a markedly enhanced susceptibility to reactive APAP metabolites presumably due to reduced GSH synthesis and thus detoxification capacity in GSH-S deficient cells. This new assay is free of detoxification enzymes such as microsomal epoxide hydrolase, requires a relatively small number of cells, and utilizes an objective, automated estimate of cell viability. It may prove useful for screening the cytotoxic potential of drugs implicated in idiosyncratic adverse reactions, and for determining the biochemical basis of susceptibility to drug toxicity.