253 CARDIOVASCULAR EFFECTS OF PANCURONIUM IN ANESTHETIZED NEONATAL PIGLETS. Norman Gootman, Barbara J. Buckley and Joy S. Nagelberg. SUNY at Stony Brook, Health Sciences Center, Division of Pediatric Cardiology, Long Island Jewish-Hillside Medical Center, New Hyde Park, N.Y. 11040

Effects of the muscular relaxant Pancuronium (P) were investigated in piglets under anesthesia with 0.25% halothane in N_2O and O_2. Artificial ventilation was adjusted to maintain normal arterial pH and PCO_2. Control values for all animals were pH 7.432±0.1 and PCO_2 34.4±1.3. Aortic pressure (AoP), heart rate (HR) and femoral and carotid flows (F) were recorded simultaneously in 17 animals in 3 age groups (6≤2 days, 5 at 1 week and 6 at 2 weeks). Resistance (R) was calculated at mean AoP/mean F. Single doses totaling 90.4±2.1 µg P/kg, which approximates the clinical dosage in infants up to 3 weeks of age, were injected into the right atrium. Different effects on AoP were observed between the ≤2 day and 2 week old piglets. AoP increased 7.9%±3.0 in the youngest and 20.5%±4.7 in the oldest. HR changes were not systematic in the youngest animals. However, HR significantly increased 17.4%±2.1 in 2 week olds. Femoral and carotid F increased in all animals while R varied. In contrast to our results with decamethonium bromide (Crane, L., et al. Arch Int. Pharmacodyn. 208:52, 1974), P never produced hypotension, thereby emphasizing P's greater clinical usefulness. (Supported by the Nassau Heart Assoc.)

254 THE PHARMACOLOGY OF 2,3-DIMERCAPTOSUCCINIC ACID (DMS) A NEW AGENT FOR THE TREATMENT OF HEAVY METAL POISONING. Joseph H. Graziano and Ernst Friedheim, Cornell University Medical College, Department of Pediatrics, New York Spon. by D. R. Miller

DMS has been identified as a potentially useful drug for the treatment of lead and mercury poisoning. Using chronically lead poisoned rats, we have compared the ability of DMS (p.o.and i.p.) to induce lead excretion to D-penicillamine, BAL, EDTA and the combination of BAL + EDTA. Each treatment group received a total drug dose of 30 mg/kg/day for 5 days and urinary and fecal lead excretion were measured daily. DMS (i.p.) and BAL (i.p.) were the most effective treatments; whereas two-thirds of the lead was excreted in the feces and one-third in urine in response to BAL, the pattern was the reverse with DMS which is more water soluble. DMS was slightly less effective when administered p.o., presumably because of incomplete drug absorption; nevertheless, this treatment was as effective as the combination of BAL + EDTA (i.p.), and more effective than EDTA or D-penicillamine.

We have extended the potential uses of DMS to include arsenic poisoning. In the rat, arsenic excretion in response to DMS(i.p) was greater than that in response to BAL (i.p.).

The LD_{50} of DMS is greater than 3 g/kg in rats and mice. The chronic administration of 100 or 200 mg/kg i.p., 5 days per week for 6 months has led to no gross or histopathology, as determined by a certified veterinary pathologist. We hope to initiate a clinical trial of DMS in the near future.

255 ENZYMATIC & GAS CHROMATOGRAPHY/MASS SPECTROMETRY ANALYSIS OF CHLORAMPHENICOL IN NEWBORN INFANTS. Jay L. Hoecker, Larry K. Pickering, Joaquin G. Liehr, Steve Kohl, Richard M. Caprioli (Spon. by R. Rodney Howell). The Univ. of Tex. Med. Sch. at Houston, Departments of Inf. Dis., Pediatr., and Biochem., Houston, Texas.

Enzymatic and gas chromatography/mass spectrometry (GC/MS) assays for chloramphenicol (CM) were developed to assist in study of the pharmacology of CM and to establish parameters for monitoring its use. An enzymatic assay based on the specific acetylation of CM with a radioactively labeled acetyl group derived from (^{14}C) acetyl coenzyme A and catalyzed using acetyltransferase prepared by two different methods was established. Results were similar when acetyltransferase enzyme prepared by either method was used. Standard curves were linear to 100 µg/ml. Six other antibiotics did not accept an acetyl group or inhibit acetylation of CM when incubated with CM at 37°C for 3 days. The enzymatic assay was compared to the GC/MS method for determination of CM in over 150 serum and CSF samples obtained from patients receiving CM. A significant correlation existed between the GC/MS and the acetylation assay ($y=1.05 x -0.20$, $r=0.998$). The sensitivity of the assays was 1 µg/ml and the precision was ±3%. Infants had dosing adjustments made to achieve peak and trough concentrations in serum of approximately 20 and 10 µg/ml. Therapeutic monitoring of CM provides a means for increasing therapeutic efficacy and avoiding toxicity in newborn infants and in patients with hepatic and renal dysfunction.

256 THEOPHYLLINE HALF-LIFE IN INFANTS AND YOUNG CHILDREN, Gregory Kadlec, Le Thanh Ha, and C. H. Jarboe (Spon. by Billy F. Andrews), University of Louisville, School of Medicine, Dept. of Pediatrics

Theophylline half-life determination kinetics were performed in 54 young children. Our patients ranged in age from three months to six years, with a mean age of 2.2 years. Mean half-life determined was 4.92 hours with a standard deviation of 1.88 hours, which is at considerable variance with previously quoted half-lives for young children. Computerized multiple regression analyses with doses of 3, 4, 5 mg/kg of theophylline every six hours were performed, and maximum, minimum, and mean steady state serum levels were developed. Five mg/kg theophylline appeared to be a safe dosage in the majority of children. Two of our subjects developed peak levels greater than 25 mcg/ml, and no toxicity was noted. Age and half-lives were compared, and there was found to be no correlation in this young age group. Theophylline half-life in young children was found to be considerably longer than previously recorded. The published values of theophylline safety range levels, e.g., less than 20 mcg/ml, need to be reconsidered.

257 REDUCTION OF OXYGEN TOXICITY BY N-ACETYL-L-CYSTEINE George H. Lambert and Raymond E. Galinsky. Univ. Penn. School of Medicine, Children's Hosp., Phila., Dept. Pediatrics and Phila., College of Pharm. & Sci., Dept. Pharmacy Practice, Philadelphia, PA (Spon. by S.J. Yaffe)

Cellular metabolism of oxygen generates various free radicals and reactive molecules. Exposure to higher than normal oxygen concentrations can damage tissue possibly via lipid peroxidation of membranes, inhibition of reversible electron transport or oxidation of SH-enzymes. Antioxidant compounds have been used successfully to protect cells from damage but their usefulness is limited because of their toxicity.

We have investigated the use of N-acetyl-L-cysteine (NAC, Mucomyst^R), a relatively non-toxic antioxidant, in preventing oxygen toxicity. Sixteen male Sprague-Dawley rats, 250-300 gm. were pretreated with one dose of NAC (1.0 mg/g i.p.) immediately prior to exposure to hyperbaric oxygen (98-100% O_2, 4 atm. absolute). Control rats (8) were pretreated with an equal volume of normal saline. The time of convulsions and time to death were used as indices of oxygen toxicity (Proc. Soc. Exp. Bio. Med. 133:103, 1970). The time to convulsions in the NAC group (298 ± 19 min; mean ± SEM) was significantly prolonged ($p<0.001$) as compared to the saline control (153 ± 13 min.). Since four of the NAC group died without seizing, the time to death was used as the time to convulsion. The time to death in the NAC group was not significantly prolonged (369 ± 23 min vs 307 ± 17 min). These data suggests that NAC may be a useful antioxidant in the reduction of oxygen toxicity.

258 DIETARY EFFECTS ON MERCURY ELIMINATION AFTER ADMINISTRATION OF CH_3HgCl OR $HgCl_2$. Timothy D. Landry, Richard A. Doherty, Allen A. Gates, Depts. of Pediatrics, Radiat. Biol./Biophysics, Obstetrics, Genetics, Environ. Health Sciences Ctr., Univ. of Rochester, Rochester, NY

Nearly 100% of CH_3Hg ingested in foods is absorbed. Thus with continued exposure, elimination rate becomes the critical determinant of CH_3Hg body burden. We have observed significant dietary effects on rates of Hg excretion. Female BALB/c mice (3-8 months of age) were fed ad libitum Pet evaporated whole milk [M], Agway RMH 3000 pelleted diet [P], or GIBCO 116EC liquid diet [G], for one week prior and two weeks subsequent to a single p.o.dose of $CH_3{}^{203}HgCl$ (0.5 mg/kg). Estimated whole body elimination half-times during 14 days after dosing were: [M]: 19.2 days (95% confidence limits:16.6-22.9); [P]: 10.6 (9.9-11.5); [G]: 5.8 (5.3-6.3). Decrease in whole body radioactivity was accurately reflected in counts recovered in excreta. Brain Hg concentrations at 14 days correlated with relative body burdens. In a similarly designed experiment female mice were dosed i.m. with $CH_3{}^{203}HgCl$ or $^{203}HgCl_2$ (0.5 mg/kg). A differential effect of diet on ^{203}Hg elimination rates was confirmed in the CH_3Hg dosed groups. However, in mice dosed with $^{203}HgCl_2$, we observed no differences in Hg whole body elimination rates between evaporated milk diet and pellet diet groups, but the GIBCO diet group showed a more rapid elimination rate. These results provide clues concerning possible mechanisms of metabolism and excretion of Hg compounds. We have shown that non-Hg dietary components can significantly affect mercury body burdens and that possible effects of diet must be considered in estimating exposure risks