301 EFFECT OF ENDOTOXIN ON HEPATIC MICROSOMAL DRUG METABOLISM OF RATS: Babasaheb R. Sonawane and Sumner J. Yaffe, Division of Clinical Pharmacology, Children's Hospital of Philadelphia and Department of Pediatrics, University of Pennsylvania.

Infections due to gram-negative bacteria have assumed ever-increasing importance during the past several years. Endotoxin, a soluble lipopolysaccharide cell wall constituent of gram negative bacteria, is released into body fluids during infection by these organisms. A key aspect in the therapeutic management of patients with endotoxemia is the administration of pharmacological agents. Since most drugs are metabolized by the hepatic mixed function oxidase system and/or by conjugation, we studied the effect of intraperitoneally administered endotoxin (a lipopolysaccaride derived from E. Coli 026B6 serotype) on hepatic microsomal drug metabolizing enzymes. Endotoxin dose response studies in adult rats resulted in a striking decrease within 24 hrs postadministration (I.P.) in hepatic microsomal aminopyrine demethylase (51.5%), benzo(a)pyrene hydroxylase (58.9%), and cytochrome P-450 (64.1%) and cytochrome b_5 (90%) of control. These changes occurred with 1 mg/kg but effects were also noted with doses as low as .1 mg/kg. Low protein diet (8%) enhanced the reduction in enzymic activity. Endotoxin administration during late pregnancy also decreased the ability of the rat to metabolize drugs. These studies emphasize the need for careful evaluation of drug administration and effects in patients with endotoxemia.

302 LETHAL AND SUBLETHAL EFFECTS ON THE PROGENY OF MALE RATS TREATED WITH METHADONE. Lester F. Soyka, John M. Peterson, and Justin M. Joffe, Univ. of Vermont College of Medicine, Department of Pharmacology, Burlington, VT

Fourteen male rats were treated with methadone HCl (METH) 10 mg/kg s.c. per day for 12 days. Fifteen control males received saline injections for four days. Each male was caged with four drug-naive females each night. METH males lost weight over the treatment period and mated less frequently. At autopsy, their seminal vesicle weight was decreased, even when corrected for body weight. Progeny of METH males (507 pups) were of lower average birth weight than controls (276). Prior copulation had a differential effect, resulting in slightly heavier control pups but significantly decreased birth weights in the METH group. Neonatal mortality of the METH progeny was 18.2%, compared to 9.5% of the controls ($P < .01$). Mortality was related in a complex fashion to number of drug exposures and previous sexual experience of the sire. Male offspring were particularly affected. Ponderal growth of survivors from litters with high neonatal death rates was diminished, with females being significantly lighter at 75 and 132 days of age. Open field defecation scores were significantly different at two but not at four months of age. No differences in acquisition of a conditioned avoidance response were noted. These results together with previous data from our laboratory establish for the first time lethal and sublethal effects on the progeny of a drug-treated sire.

303 BENZOCAINE INDUCED METHEMOGLOBINEMIA. Philip L. Townes, Martin A. Geertsma, Marie R. White. Univ. of Rochester Sch. Med. & Dent., Div. of Genetics, Rochester, N.Y.

A healthy 14 month infant developed severe cyanosis 20-30 minutes after topical application of a benzocaine containing gel administered for relief of teething discomfort. Venous blood was of brown hue; methemoglobin content was 33%. Arterial blood oxygen saturation was 64%. In the ICU, the patient made a complete recovery within 24 hours. Blood samples from the patient were subjected to extensive quantitative spectrophotometric analysis. The initial and derived spectra were characteristic of hemoglobin A. Hemoglobin M or other abnormal hemoglobins were excluded. A metabolic defect in methemoglobin reduction was excluded by measuring rates of reduction of nitrite induced methemoglobin. With these studies the patient proved to have no abnormal susceptibility for methemoglobin formation. Her acute episode occurred because the amount of methemoglobin formed exceeded her normal methemoglobin reducing capacity. Single oral doses of benzocaine administered to rats produced severe methemoglobinemia within 30 minutes. This toxicity is not direct but involves metabolic conversion of benzocaine by microsomal enzymes. There have been few prior reports of benzocaine induced methemoglobinemia. Without supporting data, it has been assumed that the hazard may be limited to infants because of their physiologic deficiency of diaphorase. This previously untested hypothesis has been excluded by our metabolic studies. PDR listings of benzocaine preparations contain no mention of this hazard. It is a hazard that deserves wider recognition.

304 ELEVATED GENTAMICIN LEVELS IN PREMATURE/AZOTEMIC NEWBORNS. Yvonne E. Vaucher*, William E. Larter*, Otto F. Sieber, Jr.*, Dept. of Pediatrics, Univ. of Arizona College of Medicine, Tucson, Arizona (Spon. by Grant Morrow III).

Peak serum gentamicin (G) levels were measured by agar diffusion 30 minutes after completion of, and trough levels just prior to, intravenous G infusion (2.4±.1mg/kg) in 44 neonates aged 14 days or less ($\bar{X}$ 5.5 days). Gestational ages (GA) ranged from 26-43 weeks ($\bar{X}$ 34.4±.7 wks). Serum half-lives ($T_{\frac{1}{2}}$), peaks, and troughs ($\bar{X}$±SEM) in 23 non-azotemic infants [BUN<15mg% and/or Creatinine (Cr)<1mg%] are presented below:

GA(wks)		$T_{\frac{1}{2}}$(hrs)	Peak(ugm/ml)	Trough(ugm/ml)
26-29	(N=5)	9.4±.6	9.8±1.4	4.2±.5
30-35	(N=5)	9.0±.6	5.7±.4 *	2.5±.2 *
36-40	(N=13)	5.5±.3 ***	5.6±.7	1.7±.2

In a group of 21 azotemic infants (BUN>15mg% and/or Cr≥1.0mg%) $T_{\frac{1}{2}}$'s and troughs were significantly elevated when compared with all non-azotemic infants:

	GA(wks)	$T_{\frac{1}{2}}$(hrs)	Peak(ugm/ml)	Trough(ugm/ml)
non-azotemic (N=23)	35.2±1.0	7.2±.5 **	6.4±.6	2.3±.3 ***
azotemic (N=21)	33.4±.8	16.1±2.8	8.2±.6	3.9±.4

(*p<.05, ** p<.01, *** p<.002)

Routine monitoring of serum G levels allows drug dosage and timing to be individualized and is particularly important in the azotemic or extremely premature neonate in whom the use of standard neonatal dosage regimens is most likely to produce excessive, potentially toxic, drug levels.

305 EFFECT OF AGE ON THEOPHYLLINE CLEARANCE AND DOSAGE REQUIREMENTS DURING CHILDHOOD. Miles Weinberger, Richard Wyatt, Leslie Hendeles, Elliot Ginchansky (Spon. by Fred Smith), University of Iowa, Department of Pediatrics, Iowa City.

Previous recommendations for weight adjusted theophylline dosage have not considered age as a contributing variable. The current data was collected in two parts. First, 23 children with chronic asthma, ages 4-15, received .8 mg/kg/hr intravenous infusions of theophylline until steady-state serum concentrations were documented. Clearance was then calculated (clearance = infusion rate ÷ steady-state serum concentration). Subsequently, 156 children with chronic asthma, ages 2½ months to 16 years, received chronic oral theophylline in 4 doses/day titrated to achieve peak serum concentrations in the therapeutic range of 10 to 20 µg/ml (mean was 15 µg/ml). Clearances among the 23 children receiving the intravenous infusion averaged 1.35 ± .46 ml/kg/min (mean ± standard deviation), but correlated inversely with age ($r_s = -.46$, $p < .025$). The 7 children over age 12 averaged .88 ± .25 ml/kg/min while the younger children averaged 1.56 ± .37 ml/kg/min. Mean oral dosage requirements also varied with age. Seventy-seven children under age 9 required 24.1 ± 5.5 mg/kg/day of theophylline to maintain therapeutic levels, and no significant correlation with age was observed in this group. Among the 79 children from 9-16 years of age, however, doses averaged 19.4 ± 4.9 mg/kg/day and correlated significantly with age ($r = -.32$, $p < .01$). Thus, weight adjusted dosage guidelines for theophylline must be age specific.

306 HIGH INCIDENCE OF A GENERALIZED EXANTHEM IN EPILEPTIC CHILDREN AND ITS RELATION TO PLASMA LEVELS OF PHENYTOIN Wilson, J.T.; Rane, A.; Höjer, B.; Thomson, G.; and Sjöqvist, F. Karolinska Institute, Huddinge Hospital, Department of Clinical Pharmacology, Stockholm, Sweden.

Phenytoin (DPH) was given in a loading dose (6mg/kg/dose x 4 then daily) or a high conventional dose (5.5-9.5 mg/kg/d) to 13 epileptic children. About 8-10 d after the first dose a generalized maculo-papular, erythematous exanthem appeared with an unexpected high frequency: 4/5 (80%) for loaded and 5/8 (63%) for high conventional doses (Wilson et al CPT 20, 48, 1976). In a prospective trial, DPH was given to ten epileptic children as either a graded dose (3 mg/kg/d x 5 days then 6 mg/kg/d) or a conventional dose (6 mg/kg/d). An exanthem was again found: 4/5 (80%) for conventional and 1/5 (20%) for graded regimen. A relationship to dose was thus apparent. Data were analysed from all patients with regard to occurence of the exanthem. Those with an exanthem showed higher average plasma levels of DPH during the first 8-14 days and higher ratio of level to dose. The ratio of total p-OH-DPH (a primary metabolite of DPH) to DPH in plasma was lower for those with a rash and who received loading or high conventional doses. Plasma protein binding of DPH showed no difference in those with or without an exanthem. A high plasma level of DPH, via dose or decreased metabolism, was associated with occurence of the exanthem. This association, here demonstrated for the first time in man, raises questions about the "toxic" vs "allergic" nature of drug associated exanthemas. (Supported by Swedish MRC 04x04496 and K4-HD42-539 from the NIH)