THE IN-VIVO EFFECT OF THEOPHYLLINE ON HISTAMINE RELEASE FROM HUMAN LEUKOCYTES. Fred Leffert,M.D., Dept.of Ped., Nat. Jewish Hospital & Research Cntr.,Denver(Intr.by Charles D. May, M.D.)

The antigen-induced release of mediators from sensitized cells is an active secretory process, inhibited by drugs such as theophylline, which increase intracellular cyclic adenosine monophosphate concentration. This inhibition has been demonstrated in several in-vitro systems, but at concentrations ($\geq$ 18μg/ml) which might not be achieved in vivo with the dosage commonly employed in treatment of asthma. This study investigated the possibility that theophylline, as commonly used for asthma therapy, might also inhibit mediator release. 7 atopic subjects (6 asthmatic children and an adult with hayfever) had leukocyte histamine release determined with antigens to which they were sensitive. Release was measured at 8 a.m. and 12 noon on 2 control days and on a drug day, on which theophylline 6mg/kg was given orally at 8 a.m. Plasma theophylline levels were determined on each specimen of blood drawn for histamine release. 3 subjects had up to 38% inhibition of histamine release by theophylline; the other 4 patients showed no effect. 2 of the 3 subjects who showed inhibition had plasma theophylline levels in excess of 10μg/ml; all of the unresponsive subjects had levels less than 10μg/ml. The plasma level achieved by a given dose of theophylline is extremely variable among patients, but in some patients levels are achieved which will inhibit mediator release. This suggests that in some asthmatic children theophylline may have beneficial effects other than bronchodilatation.

RELATIONSHIP BETWEEN DOSE AND APPARENT VOLUME OF DISTRIBUTION OF SALICYLATE IN CHILDREN. Gerhard Levy and Sumner J. Yaffe, Departments of Pharmaceutics and Pediatrics, State University of New York at Buffalo.

The purpose of this investigation was to determine the relationship between dose and the distribution of salicylate in the body. The apparent volume of distribution was determined from the concentration of salicylate in plasma or serum at various times after salicylate ingestion and from the amount of drug remaining in the body at these times as assessed from urinary excretion data. These studies were carried out on eleven children, 4 months to 16 years old, who had ingested from about 36 to over 340 mg. salicylic acid (mainly as aspirin) per kg. of body weight. The apparent volume of distribution of salicylate ranged from 162 to 345 ml./kg. and increased with increasing dose. This means that plasma salicylate concentrations in children who have ingested large doses of the drug are proportionately not as high as those in children who ingested lower doses of salicylate. These observations help to rationalize the use of the Done nomogram (which involves estimation of initial salicylate concentrations by back extrapolation) to assess the severity of salicylate intoxication on the basis of plasma salicylate concentrations. (Supported in part by grants GM19568 and RR-628 from the National Institutes of Health)

EPINEPHRINE (E) SECRETION IN THE RAT FETUS IN RESPONSE TO NICOTINE ADMINISTERED TRANSPLACENTALLY - RESISTANCE TO CHANGE OF FETAL PLASMA LIPIDS. H. David Mosier, Jr., Carmen C. Capodanno, Ivy O. W. Li, Caroline Sue Magruder, and Regina A. Jansons. Univ. Calif. (Irvine) Col. Med., Dept. Ped., and Memorial Hosp. Med. Ctr., Long Beach, California.

We have shown previously that nicotine readily crosses the rat placenta. The present experiments were undertaken to determine whether nicotine causes catecholamine release by the feat rat adrenal, and whether acute or chronic dosage of the fetus with nicotine causes lipid increases in fetal plasma. Pregnant Long-Evans rats were fed stock diets containing 0.05 or 0.1 mg/g added nicotine during 10-20 or 0-20 d of pregnancy. Control rats were fed stock diet during 0-20 d. Mean nicotine intake ranged up to 6.03 mg/kg/d. No significant changes occurred in fetal plasma on day 20 with respect to triglyceride (TG), P-lipid or cholesterol levels. Pregnant rats were given single doses of 1 mg/kg nicotine ip on day 20. Maternal plasma free fatty acids (FFA) and TG rose, but fetal values did not change. Fetal adrenal E content decreased after nicotine injection and then rose to slightly higher than control values. There was no decrease after saline injection. The results indicate that the fetal adrenal of the rat secretes E in response to nicotine entering the fetus transplacentally. The resistance of fetal FFA to change after nicotine is probably due to resistance to E induced elevation of FFA. The placenta may be responsible for maintaining the steady state of fetal plasma lipids.

LIPOLYTIC ACTION OF L-CARNITINE IN VITRO IN HUMAN NEWBORN SUBCUTANEOUS ADIPOSE TISSUE. Milan Novak*, Duna Penn-Walker and Ellen Monkus, Dept. of Ped., Univ. of Miami Sch. of Med., Miami, Fla.

Oxidation of fatty acids is a major pathway supporting energy requiring processes in the early postnatal period. This is documented by an increase in free fatty acids (FFA), glycerol and ketone bodies in the blood. FFA and glycerol arise from intensive triglyceride breakdown in white adipose tissue. Activation of lipolysis requires ATP. Decreased lipolysis is seen in vitro after the first 24-48 hr of life. Since FFA can uncouple mitochondrial respiration, the early accumulation of FFA known to occur in adipose tissue could lead to a secondary depression of lipolysis due to inadequate ATP generation.

Carnitine acts as a coupling agent in mammalian brown fat mitochondria. Its effect on lipolysis (glycerol release) was measured in fragments of human newborn and adult subcutaneous (white) adipose tissue. In the neonate, L-carnitine (2.5mM) enhanced glycerol release with or without stimulation by a phosphodiesterase inhibitor (theophylline, 10^{-3}M) or a beta-agonist (isoproterenol, 10^{-5}M)($p \leq 0.05$); deoxycarnitine (2.5mM) decreased lipolysis under similar conditions ($p \leq 0.05$). In the adult, L-carnitine increased lipolysis only in presence of isoproterenol ($p \leq 0.05$) while deoxycarnitine had no effect.

Carnitine is contained in milk. These studies suggest a deficiency of carnitine might decrease the availability of FFA as fuel for essential metabolic needs, particularly in the small or ill neonate with inadequate oral intake.

A STUDY OF FACTORS THAT INFLUENCE THE SEVERITY OF NEONATAL NARCOTIC WITHDRAWAL. E.M. Ostrea, Jr., C.J. Chavez & M.E. Strauss Wayne State Univ., Hutzel Hosp. & Children's Hosp. of Mich., Depts. Peds. & Psychol., Detroit, Michigan. (Intr. by P.V.Woolley, Jr.)

A prospective study of 198 infants of drug dependent mothers included: (1) history of maternal drug habit, (2) measurement in infant's urine of total morphine & qualitative detection of other drugs by gas chromatograph, (3) evaluation of severity of neonatal withdrawal by a scoring system & (4) study of the effect of a modified environment (quiet, warm, dimly lit & frequent feeding) on withdrawal.

RESULTS: (1) history is unreliable in assessing maternal drug habit. Mean morphine levels of 1.02 & 0.99 mg% were found in the urine of infants whose mothers claim non-usage of heroin for 1-3 months before delivery, respectively. (2) severity of neonatal withdrawal did not correlate with infant's urine morphine level (range 0-9.4 mg%, $P < 0.35$), but correlated significantly to maternal methadone dose ($P < 0.005$). None to mild withdrawal was seen in mean maternal methadone dose of 21.9 mg/day vs. 31 mg/day in moderate to severe withdrawal. The duration of methadone intake did not correlate with severity of withdrawal. (3) in order of decreasing frequency the S & S of withdrawal were: fist-sucking, irritability, tremors, sneezing, shrill cry, hypertonia, stuffy nose, sweating, diarrhea, vomiting and yawning. Convulsion was not noted. No death occurred. Mean birthweight = 2885 ± 454 g & gest. age = 39 ± 1.1 wks, (>10th percentile). Mean weight loss = 160.5 g (4) the control (C) & experimental (E) groups for modified environment study were matched for weight, sex, gest. age and maternal methadone dose. The incidence of mild withdrawal was 68% (C) vs. 71% (E); of moderate withdrawal, 27% (C) vs. 26% (E); of severe withdrawal, 5% (C) vs. 3% (E). The difference between the 2 groups was not significant. (5) the qualitative detection of other drugs in the infant's urine will be presented.

EFFECT OF ALBUMIN AND DRUG CONCENTRATION ON THE BINDING OF FUROSEMIDE. Jozef Prandota and Albert W. Pruitt, (Intr. by R.W. Blumberg), Emory University School of Medicine, Department of Pediatrics and Clinical Pharmacology Program, Atlanta.

Furosemide is 95% bound to human plasma (Kelly, et al., Clin. Res. 21:199, 1973); however, factors influencing that binding have not been evaluated. The binding of furosemide-^{14}C (carboxyl-^{14}C) to human albumin and plasma was investigated by equilibrium dialysis at 37°C for 18-24 hours. Binding of furosemide (3.4 ug/ml) to varying concentrations of human albumin decreased slightly from 97.2% (5 gm% albumin) to 95.8% (2 gm%). However, albumin concentrations less than this showed a greater decrease in binding to 89.6% (0.5 gm% albumin).

Using 4 gm% human albumin, binding of the drug decreased from 97% to 89% as furosemide concentration was increased from 1.8 ug/ml to 600 ug/ml. Furosemide (4 ug/ml) was not displaced by diphenylhydantoin, phenobarbital, diazoxide, trifluoperazine or chloramphenicol in therapeutic concentrations.

Influence of albumin concentration on the binding of furosemide was evaluated in plasma from 3 children with nephrotic syndrome. The albumin concentration was 0.6, 1.1 and 1.8 gm% and the respective binding of furosemide was 93, 90 and 95%.

These findings demonstrate that this diuretic is highly bound to plasma albumin, and the free drug fraction may be affected by both the dose and the patient's plasma albumin concentration.