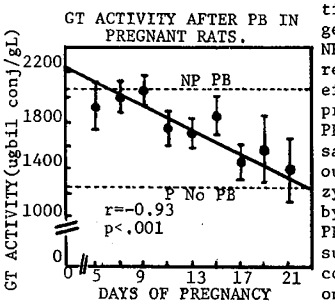
HEME SYNTHESIS AND MICROSOMAL MIXED FUNCTION OXIDATION IN HUMAN FETAL TISSUES. Arleen Rifkind, Niels Lauersen, Soja Bennett and Maria New. Cornell Univ. Med. Coll., Dept. Ped., New York City

Knowledge of fetal drug metabolism is a necessary prerequisite for determining the safe and rational use of drug therapy during pregnancy. Heme synthesis and drug metabolism were studied in 40 human fetuses aborted by hysterotomy and prostaglandins. Δ aminolevulinic acid synthetase (ALAS), the rate limiting enzyme in heme synthesis, could be measured in livers and adrenals of fetuses aborted by hysterotomy but not in fetuses aborted by prostaglandins. Mean levels of ALAS ± SE were 74.3 ± 6.4 mμmol/gm liver in 5 fetuses aborted by hysterotomy. Aryl hydrocarbon hydroxylase activity (AHH) was highest in the adrenal gland and progressively lower in liver, intestine, testes, kidney and lung in fetuses from both groups. AHH activity in the adrenal gland was positively correlated with the concentration of microsomal cytochrome P-448 and negatively correlated with the concentration of cytochrome P-420. Secobarbital when added to human fetal liver and adrenal microsomes resulted in a type II difference spectrum (peak 430 nm, trough 406 nm) although when added to microsomes from chick embryos a type I spectrum (peak 385 nm, trough 419 nm) resulted. These studies 1) supply the first reported measurements of ALAS in human fetal tissues, 2) show that fetuses aborted by prostaglandins are useful for studies of AHH activity, 3) provide evidence that AHH in the fetal adrenal is mediated by cytochrome P-448 and 4) show species differences in substrate binding to embryonic microsomal proteins.

DIMINISHED RESPONSE OF HEPATIC GLUCURONYL-TRANSFERASE TO PHENOBARBITAL DURING PREGNANCY. S. Vaisman and L.M. Gartner, Dept. of Ped., Albert Einstein Coll. of Med., Bronx, N.Y.

Bilirubin (B) glucuronyl-transferase (GT) activity was studied in liver homogenates of pregnant (P) and non-pregnant (NP) female rats. Activity in NP rats was 1286±166(S.D.) ug B conjugated/g liver/40 min (N=13) and in P rats (5 to 21 days gestation) was 1271±211 (N=43). No change in maternal liver GT activity was observed during pregnancy. Administration of phenobarbital (PB)(100mg/Kg) to 6 NP rats for 3 days increased GT activity to 2061±208 (62%). Similar treatment of 47 P rats resulted in progressive decrease in GT stimulation as a function of increasing days of gestation (figure). In P and NP rats, 3 days PB treatment resulted in no increase in either liver weight or liver protein concentration. Hepatic PB concentrations were the same in NP and in P throughout pregnancy. Thus, base enzyme activity was not altered by pregnancy but response to PB stimulation was reduced suggesting a previously unrecognized effect of pregnancy on enzyme induction.



MEASUREMENT OF BRAIN BILIRUBIN IN GUNN RATS AND THE EFFECT OF ASPHYXIA AND SULFADIMETHOXINE. Arthur L. Rose, Vivian Zaby and Morris B. Abramson (Intr. by Dr. Lawrence Gartner), Albert Einstein College of Med., Dept. Neurol., Bronx, N. Y.

Gunn rat encephalopathy is attributed to the toxic action of bilirubin but the brain bilirubin content of young rats has not been previously measured. Homozygous infant rats are usually healthy and their brains do not show any visible yellow discoloration although extensive neuronal degeneration is constantly present (Rose & Johnson, 1972). Bilirubin contents has been determined by light absorption at 453nm of chloroform: acetic acid (6:1) extracts of the brains in four groups of 14 day old rats:

Group I	(n=10)	Untreated controls	1-3ug per brain
Group II	"	Asphyxia	1-3ug " "
Group III	"	Sulfadimethoxine *	4-7ug " "
Group IV	"	Asphyxia and sulfadimethoxine*	10-22ug " "

These data show that (a) in Gunn rats the loss of neurons occurs even when only trace amounts of bilirubin are present in the CNS; (b) the increased entry of bilirubin into the brain following injection of sulfadimethoxine is further augmented by asphyxia. (Supported by NIH Grant 1ROL NS 09064)
*100mgs/kg i.p. injection.

AGE-DEPENDENT ELIMINATION OF HEXACHLOROPHENE (HCP) IN NEONATAL RODENTS: POSSIBLE ROLE OF ENTEROHEPATIC RECIRCULATION. M.Warner*, B.Hales*, H.Yang*, L.Chung* and A.Neims. Depts. of Pharmacol. & Ped., Roche Dev. Pharmacol. Unit, McGill Univ. and Montreal Children's Hosp., Montreal, Canada.

We have described previously an increased sensitivity of immature rodents to HCP, a finding which may relate to the reported high incidence of suggestive neuropathological changes found in exposed low-birth-weight infants. This age-dependent sensitivity in rodents can be accounted for by slower elimination of HCP. In adult rats and mice, biliary excretion accounts almost quantitatively for elimination of ^{14}C-HCP, with 98% of label in bile present as the monoglucuronide (HCP-G). HCP-G is identified by chemical and enzymatic hydrolyses, and mass spectral analysis. Elimination of HCP from plasma is 6-fold slower in 3-day-old animals, yet bile and small intestinal contents exhibit comparable concentrations of radioactivity. Surprisingly, in the neonate 90% of label in bile is HCP, not HCP-G. The radiolabel in livers from young and adult rodents is primarily HCP. Adult-type elimination and biliary compositions are approached by 2 weeks of age. These results are compatible with an important contribution of enterohepatic circulation to the overall pharmacokinetic profile of HCP in immature rodents. (Supported in part by the MRC of Canada.)

NEONATAL METHADONE WITHDRAWAL SYNDROME: CORRELATION WITH PLASMA METHADONE CONCENTRATION AND MATERNAL METHADONE DOSAGE. Tove S. Rosen, M.D., Charles E. Pippenger, Ph.D., Depts. of Pediatrics and Neurology, Columbia University, College of Physicians and Surgeons, N.Y., Intr. by L. Stanley James, M.D.

The relationships between maternal dose of methadone and neonatal withdrawal, and between neonatal plasma levels of methadone ([M]) and symptomatology have been investigated. Methadone was analyzed by gas chromatography; recovery was 88-94 % in the 0.1-1.0 ug/ml range. Ten mothers and their neonates were studied: 3 mothers were taking methadone 10 mg/day and 5, 40-60 mg/day; 2 mothers were detoxified during the 3rd trimester of pregnancy. All 8 infants of mothers on methadone exhibited withdrawal; 3 had no detectable[M]in the 1st 24 hours of life; 2 of these began withdrawal in the 1st few hours of life and the 3rd after 24 hours. In the other 5 symptomatic infants [M]at birth = 0.07-.14 ug/ml; in 4,[M]= 0-.06 ug/ml after 24 hours, at which time withdrawal began, and the 5th had[M]=0.12 ug/ml at 24 hours with no detectable[M]at 48 hours. Withdrawal commenced in this infant shortly thereafter. Neither infant of the detoxified mothers developed withdrawal nor had they any detectable[M]at birth. Thus there appears to be no relationship between maternal dosages of methadone (10-60 mg/day) and the time of onset of neonatal withdrawal. Infants born to mothers who are drug-free in the 3rd trimester do not withdraw. Newborns with[M]=.07-.14 ug/ml do not withdraw: withdrawal begins when[M]falls to 0-.06 ug/ml.

BILE SALT METABOLISM IN THE PREMATURE INFANT: INFLUENCE OF PRENATAL DEXAMETHASONE AND PHENOBARBITAL. J.B. Watkins, P. Szczepanik, J.B. Gould, P. Klein, and R. Lester, Boston Univ. Sch. Med., Children's Hosp. Med. Ctr., Dept. of Ped., and Argonne Nat. Lab., Argonne, Ill. (Intr. by R.J. Grand).

Bile salt synthesis and pool size were determined by stable isotope dilution in 9 healthy premature infants of 32-36 wk gestation. In one group (4 infants), the mothers had received dexamethasone (3) or phenobarbital (1) prior to delivery; the other mothers had received no drugs. For infants of the treated mothers, total bile salt pool was 79 ± 20 mg (avg ± SE) and synthesis was 27 ± 5 mg/da; whereas in infants of untreated mothers, total bile salt pool was 20 ± 2 mg and synthesis was 8 ± 1 mg/da. When normalized for surface area, the cholic acid pool in the treated group was 321 ± 117 mg/M^2 and synthesis was 98 ± 35 mg/M^2/da, values equal to those obtained in full-term infants and 4 times those in the group with untreated mothers. Intraduodenal bile salt concentrations during meals in the treated group were 5.3 mM vs 1.2 mM for the untreated group, an increase associated with improved dietary lipid absorption to >90% of intake in 3 of 4 infants. Conclusions: (1) Premature infants have immature bile salt metabolism as demonstrated by reduced pool size and synthesis rates with intraduodenal bile salt concentrations below levels required for the complete solubilization of lipid. (2) Prenatal administration of dexamethasone or phenobarbital produces precocious maturation of these parameters and thus may profoundly influence the postnatal nutrition of the premature infant.