377 DEVELOPMENTAL INCREASE IN THE CARDIAC CHRONOTROPIC RESPONSE TO ISOPROTERENOL (IS). RM Ward, BL Mirkin, S Singh and C Daniels. Penn State Univ Coll of Med, M. S. Hershey Med Ctr, Dept of Peds, Hershey, PA. Univ of Minnesota Hospitals, Dept of Clin Pharmacol, Minneapolis, MN.

The ovine chronotropic response to injection of catecholamines is reported to increase during gestation, exhibit denervation supersensitivity, but is similar to the adult after birth. This study examined the developmental changes in the heart rate response to beta adrenergic stimulation with IS. Dose response studies were carried out in chronically catheterized, sheep -- 5 near-term fetuses, 4 newborn, and 5 pregnant adults. IS was infused for 15-30 min until a steady state response was obtained for each dosage of the series. Results are shown below.

ISOPROTERENOL DOSE	% CHANGE HEART RATE (mean±SEM)		
(µg/kg/min)	Fetus	Newborn	Adult
0.010			27.4±3.8
0.025		17.8±2.7	50.8±6.9
0.050	11.9±4.8	35.8±4.4	92.8±7.0
0.100	26.1±5.1	45.0±3.8	111.5±9.9
0.250	36.3±3.6	52.5	
0.500	69.8±8.7		

These studies indicate that the ovine chronotropic response to beta adrenergic stimulation increases not only during gestation but from the newborn period to adulthood. This may represent a maturational increase in cardiac beta receptor number, affinity or responsiveness.

● **378** ONTOGENY OF β-ADRENERGIC RECEPTORS IN MAMMALIAN LUNG. J.A. Whitsett, Dept. Peds. Cincinnati, O.

The ontogeny of β-adrenergic receptors (BAR) in lung was described in the rabbit, rat, sheep and guinea pig. Developmental increases in binding capacity were demonstrated in all species, for example, rabbit lung membrane bound (-)-[^{3}H]-dihydroalprenolol, [^{3}H]DHA to a single class of sites, was stereoselective, reversible and saturable; K_D 1.78±0.30 nM. Binding at all ages was inhibited by agonists in the order of potency: Iso > Epi=Norepi characteristic of a β_1AR subtype. Studies with metoprolol (β_1) and zinterol (β_2-selective) revealed 60% β_1- and 40% $\beta_2$adrenergic subtypes at all ages. Bmax increased 11.5 fold from day 25 of gestation to adulthood, increasing during the latter days of gestation and the early neonatal period, from 37±10 fmolemg^{-1} protein to 425±51 in the adult, m±SD. Gpp(NH)p decreased agonist affinity more effectively in adult than in fetal lung and we hypothesize that a "coupling" defect exists in fetal lung BAR. The sensitivity of adenylate cyclase activity to catecholamine was maximal in adult rabbit lung increasing with age from 23% at day 25 gestation to 255% stimulation in the adult. Pulmonary BAR numbers at term gestation were higher in animals which are relatively more mature at birth (guinea pig and sheep) as compared to less mature (rabbit and rat). In conclusion, β-adrenergic receptors appear to be a sensitive indicator of pulmonary maturation and the increase in BAR during development in mammalian lung and supports the role of β-adrenergic receptors in the regulation of pulmonary function.

379 PHARMACOKINETICS OF PIPERACILLIN IN INFANTS AND CHILDREN. Chris B. Wilson, Terry L. Stull, Kent Opheim, Jeff Koup, Lee Adelman, Arnold L. Smith. Univ. of Wash. Sch. of Med. Dept. of Peds/ Child. Ortho. Hosp. Seattle, WA

Piperacillin (PIP) is a new penicillin derivative with enhanced activity against gram-negative organisms. We evaluated the pharmacokinetics of this compound in 13 children (ages 1.1-12.7 years). 5 children had Pseudomonas infections (3 osteitis, 1 urinary tract infection, 1 peritonitis). 1 child had foot cellulitis and the remaining 8 had fever and neutropenia. Piperacillin was administered by constant 30 min. intravenous infusion; blood was collected at the end of the infusion and 30, 60, 90 and 120 min. thereafter. The concentration of Piperacillin in serum was determined by a newly developed HPLC assay. The data appeared to fit a one compartment model with first order kinetics. Preliminary results from patients with normal renal function revealed a narrow range of serum half-life ($T_{½}$); 25.7 to 32.2 min. The apparent volume of distribution (Vd) varied from 0.19 to 0.35 L/Kg. Total body clearance (Cl_B) varied from 155 to 361 ml/min/1.73m^2; Cl_B correlated directly with creatinine clearance (r=.87) In one patient with renal failure (Creat. clear = 6.9 ml/min/1.73m^2) the $T_{½}$ (70.6 min) was prolonged and the Cl_B (104 ml/min/1.73m^2) was slightly decreased. This suggests that PIP is eliminated both by renal excretion and by non-renal mechanisms; determinations of urinary excretion and renal clearance of PIP are in progress. These initial data suggest that a desired peak concentration of 150 µg/ml can be achieved with an average dose of 55 mg/Kg; drug accumulation does not occur with dosing intervals of 4 hours in patients with normal renal function.

380 PENETRANCE OF NAFCILLIN INTO HUMAN VENTRICULAR FLUID: CORRELATION WITH VENTRICULAR PLEOCYTOSIS AND GLUCOSE LEVELS. Ram Yogev, William E. Schultz, and Sanford B. Rosenman (spon. by Stanford T. Shulman). Northwestern Univ. Medical School, Children's Memorial Hospital, Chicago, and Wyeth Laboratories, Radnor, Pennsylvania.

Hydrocephalic patients with shunts are prone to infections with Staphylococcus epidermidis and S. aureus. Nafcillin represents an antibiotic of choice for treatment of such infections because limited data suggest that it penetrates well into the ventricular fluid in the presence of inflammation. Fourteen hydrocephalic children with suspected shunt infections were studied for penetrance of nafcillin into ventricular fluid following intravenous administration. In seven patients with bacterial ventriculitis, 6.7±2.6% of the peak serum level was detected in the ventricular fluid. In the remaining seven patients without bacterial ventriculitis, a lower percentage of peak serum levels was detected in the ventricular fluid (1.32±0.64%). The degree of ventricular pleocytosis was poorly correlated with penetrance of nafcillin (r=0.1343, p=NS). In marked contrast, a strong inverse correlation was present between ventricular fluid glucose levels and penetrance of nafcillin (r=-0.7275, $p<0.001$). All patients with normal glucose levels had a very low level of nafcillin. These results suggest that penetrance of nafcillin into ventricular fluid is linked in an inverse fashion to the mechanism(s) controlling ventricular fluid glucose concentrations.

381 EFFECTS OF MATERNAL RITODRINE THERAPY ON FETAL RAT BRAIN DEVELOPMENT. Ehud Zmora and Donald L. Shapiro. University of Rochester., School of Medicine, Strong Memorial Hospital Department of Pediatrics, Rochester, NY

Ritrodrine is a beta-adrenergic agonist used for the inhibition of pre-term labor. As a potential activator of the cyclic AMP system, biochemical changes in the fetus might be anticipated after maternal treatment. Effects of maternal treatment with ritodrine on fetal rat brain development were investigated. A long-term treatment group (L) received ritodrine,3mg/kg/dose,IM q8h on days 18-22 of pregnancy.A short term treatment group (S) received one 3mg/kg I.V.dose on day 22. Controls for L and S received saline by the same procedures.Pups were delivered by C/section on day 22. Their body and brain weights and brain protein, DNA,cholesterol, glycogen,myelin basic protein and beta-adrenergic receptors (by binding of Dihydroalprenolol,DHA) were measured. No statistically significant changes were detected.Using this experimental model, there seem to be no adverse biochemical effects of Ritodrine on fetal rat brain development.

RESULTS (± S.E.)

	brain weight gm	Mg protein/ gm brain	µgm Cholesterol/ mg protein	µgm glycogen/ mg protein	pmoles DHA bound/mg brain
L	261±7	69.8±4.0	23.8±1.7	51.0±4.7	440±130
L-Control	252±9	68.1±6.6	24.3±2.0	48.7±5.3	480±110
S	253±6	74.4±2.1	22.7±1.3	48.8±4.6	-
S-Control	263±10	73.0±2.9	23.2±1.2	51.8±4.3	-

ENDOCRINOLOGY

382 OXYTOCIN RHYTHM IN PRIMATE CSF. Henry G. Artman, Steven M. Reppert, Mark J. Perlow, Subbiah Swaminathan David C. Klein, Delbert A. Fisher, UCLA School of Medicine, Harbor-UCLA Medical Ctr., Dept. of Pediatrics, Torrance, CA Massachusetts General Hospital, Boston, Mt. Sinai Hospital, New York, NIH, Bethesda.

Little is known about the function of oxytocin (OT) in males. We have recently observed a diurnal rhythm of OT levels in adult male monkey CSF. In the present study we determined whether altered lighting patterns would affect this rhythm.

Four male rhesus monkeys (5.5-6.5 kg) were adapted to chronic restraint primate chairs. Polyethylene catheters were threaded via a spinal needle from the lumbosacral area cephalad in the subarachnoid space. CSF was withdrawn continuously by peristatic pump at a rate of 1 ml/hr and collected as 2 hr samples. OT was measured in CSF by radioimmunoassay without extraction. Recovery of added OT in pooled monkey CSF was 73-89%. As expected, there was a 3-7 fold increase in CSF OT concentrations during the day relative to nighttime values. In monkeys kept in light/dark of 12 hr/12 hr, nighttime OT concentrations ranged from 2-10 µU/ml; daytime concentrations ranged from 7-60 µU/ml. This pattern persisted despite constant light or dark for 72 hrs with no significant change in the rhythm or its relationship to time of day.

These results suggested that the CSF OT rhythm is endogenously generated. Perlow et al have shown that blood levels of OT in rhesus monkeys show no rhythmic pattern. The organized rhythm of OT confined to the CSF suggests that OT may have a separate function in the nervous system as a neuroendocrine transmitter.